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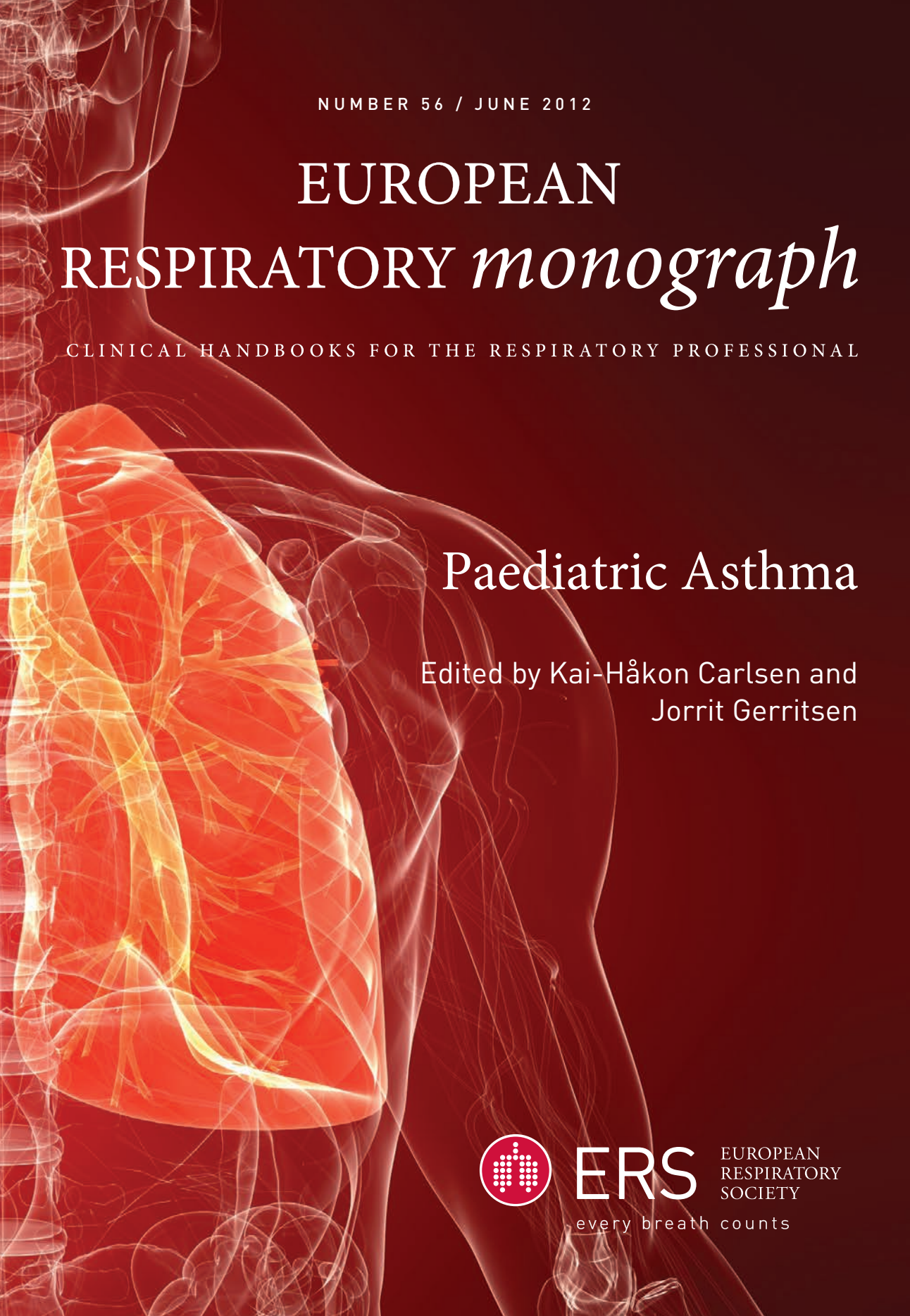

Paediatric Asthma

Edited by Kai-Håkon Carlsen and Jorrit Gerritsen

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every breath counts

European Respiratory Monograph 56, June 2012

Paediatric Asthma

Edited by Kai-Håkon Carlsen and Jorrit Gerritsen

Editor in Chief
Tobias Welte

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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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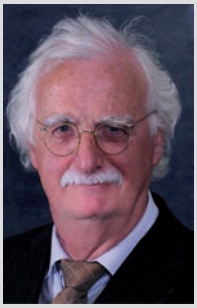
Guest Editors

Kai-Håkon Carlsen

Kai-Håkon Carlsen is Professor of Paediatric Respiratory Medicine and Allergology at the University of Oslo (Oslo, Norway), senior consultant of the Paediatric Clinic of Oslo University Hospital and Professor of Sports Medicine at the Norwegian School of Sports Sciences (Oslo). He was President of the European Paediatric Respiratory Society (1991–1993), President of the Norwegian Society of Allergy and Immunopathology (1989–1993), Head of the Paediatric Assembly of the European Respiratory Society (ERS) (1997–2001), Chair of the ERS School (2002–2005) and Chair of the European Lung Foundation (2007–2010). He has also been an Associate Editor of the European Respiratory Journal (*ERJ*) (1998–2003), an Associate Editor of *Acta Paediatrica* (2008–2011) and a member of the editorial board of *Allergy* (1999–2011). He has been a member of the editorial board of *Paediatric Allergy and Immunology* since October 1997. Kai-Håkon was also a member of the editorial board of *Paediatric Pulmonology* (1997–2004) and the first Chief Editor of *Breathe*, the educational journal of the ERS (2004–2005). He gave the prestigious Jean-Claude Yernault Lecture at the ERS Annual Congress in September 2007 and received the Life Time Achievement Award of the Paediatric Assembly of the ERS in 2010. Kai-Håkon is presently a member of the Tobacco Control Committee of the American Thoracic Society (ATS), has been a member of several Task Forces of the ERS, ATS and the European Academy of Allergy and Clinical Immunology (EAACI), and is presently part of the ERS/ATS Task Force on Bronchial Hyperresponsiveness, the ERS Task Force on Rare Lung Diseases and the Paediatric Asthma ICON Task Force of EAACI.



Jorrit Gerritsen

Jorrit Gerritsen served as Secretary and Head of the Paediatric Assembly of the ERS, and was President of the ERS from 2009 to 2010. He has been involved in follow-up studies of asthma from childhood to adulthood, epidemiological studies, studies on the role of the environment, the large Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort study, studies on genetics of asthma and studies on cystic fibrosis. He was Editor of the *Dutch Paediatric Journal* and several other respiratory journals, and is an Associate Editor of the *ERJ*. He has been involved, as first author or as co-author, in more than 220 peer-reviewed international publications, has published several books, and has participated in writing chapters of international books.

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Preface

There is no question about it: in terms of morbidity and healthcare costs, asthma is the most important respiratory disease in children and adolescents. Both research and clinical development have been tremendously successful over the last few decades, and understanding about the genetics, molecular biology, pathophysiology and clinical implications of asthma have been greatly improved. We have become aware that paediatric asthma is not a homogenous disease, but is very heterogeneous, with various clinical phenotypes that need different diagnostic and therapeutic approaches. Like bronchial malignancy, asthma may be one of the first diseases in which personalised, phenotype-driven medicine could be possible in the next few years. However, such an approach will not only have medical implications but will raise a number of questions with regard to educational programmes for physicians and patients, and will give a focus on pharmacoeconomic considerations.

Asthma research driven by paediatricians has produced impressive results in the past, and this will also be the case in the future. The winners of all of these ongoing efforts are the patients, as good research leads to better care with an improved quality of life.

This issue of the *European Respiratory Monograph* summarises the current knowledge on paediatric asthma but also focuses on future developments. I want to congratulate the Guest Editors for this excellent *Monograph*, which should be of interest to paediatricians but also to general medical doctors and pulmonary specialists treating adults. I am convinced that they will find this *Monograph* useful in daily practice.

Editor in Chief
Tobias Welte

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Introduction

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Paediatric asthma remains a health problem on a global scale, for the health systems of individual countries, for the families of asthmatic children and for the asthmatic children themselves. At present, we have no cure for asthma, and paediatric asthma most often represents a lifelong problem, although modern and optimal treatment do offer good disease control; most children with asthma are able to have a "healthy" life, and participate in physical activities on an equal level with their healthy peers, with a normal development into adolescence and adulthood.

One major problem of paediatric asthma is the "lifelong" aspect. Recently, paediatric asthma has been reported as a major risk factor for chronic obstructive pulmonary disease (COPD) in adult life, thus underlining the need for early diagnosis, optimal treatment and monitoring of paediatric asthma.

This issue of the *European Respiratory Monograph* covers the different aspects of paediatric asthma. The many phenotypes of asthma with different clinical characteristics at different ages illustrate the heterogeneity of paediatric asthma. These include different levels of severity and, in particular, problematic severe asthma. Many different causative factors have a role in the pathogenesis of asthma and influence the clinical presentation. These include: food allergy; viral and bacterial infections; allergen exposure and exposure to indoor and outdoor pollutants; psychological factors; and physical activity and sports. The genetics of asthma is complicated, and epigenetics may help explain the increase in prevalence over recent decades.

The care and treatment of asthmatic children is one of the major tasks of paediatric respiratory medicine. There are different approaches to the treatment of asthma at different ages, and acute asthma requires particular concern and treatment strategies. Monitoring and follow-up of paediatric asthma remain important for optimal treatment.

All these aspects of handling paediatric asthma, as well as the many faces of paediatric asthma, are thoroughly discussed by distinguished paediatric pulmonologists in this issue of the *European Respiratory Monograph*. We hope that our young colleagues will find this Monograph useful in the clinical setting and that it will remain an inspiration in their future research.

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Chapter 1

Asthma in children: the road to individual asthma phenotypes

Karin C. Lødrup Carlsen[*,#] *and Kai-Håkon Carlsen*[*,#,¶]

SUMMARY: The childhood asthma prevalence increase, during recent decades, may represent a shift in distribution of asthma phenotypes. The lung meets the external environment directly through the airways, as well as indirectly, by way of circulatory, neural and immunological responses. However, it is not clear how, and to what extent, environmental factors together with constitutional and genetic factors co-act to result in asthma and define asthma severity. Despite decades of research there has not been a significant breakthrough in understanding the mechanisms, genetics, therapeutic interventions and possible preventive strategies of asthma. Thus, we still lack significant knowledge that could help target asthmatic children with optimal management or ultimately prevent asthma developing. These gaps in knowledge are likely to stem from our inability to identify relevant sub-groups of childhood asthma, or even to define asthma in a reasonably objective manner. The present chapter will briefly describe the importance of characterising childhood asthma phenotypes and approaches that have been and are currently undertaken to identify them.

KEYWORDS: Allergy, asthma, birth cohorts, child, phenotypes, statistics

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The childhood asthma disease spectrum is well recognised [1–3]. However, sub-groups are challenging to identify, define and use as a base for therapeutic considerations. At present we lack clear definitions for making an asthma diagnosis, particularly in the youngest children. Furthermore, it is challenging to identify early asthma from other wheezy disorders in preschool children, as well as defining optimal treatment options in this age group. These uncertainties probably reflect the current lack of understanding of the underlying pathophysiological mechanisms. Not only do we acknowledge that asthma is a heterogeneous disease [1, 4, 5], but even the relationship with other allergic diseases, as well as with allergic sensitisation, is unclear. This has resulted in an increasing number of papers approaching phenotype descriptions [6]. Thus, a need to rethink scientific approaches to understand these issues has led to new statistical approaches. Large collaborative research programmes, such as the MeDALL (Mechanisms of the

Development of ALLergy, Grant Agreement) [7], will use novel integrated approaches to answer some of these questions. However, what are the questions?

How many asthma types are there?

Clearly, nobody knows the answer to this at present. Several approaches have been attempted in the search for childhood asthma phenotypes. Starting with the traditional way of categorising, which is the presence or absence of allergic sensitisation (''allergic'' asthma), through to various time-presentations of ''wheezy'' phenotypes or a combination of these; severity of disease; intermediate phenotypic or asthmatic traits; and down to current statistical clustering methods [8]. The current focus is to free the analyses of information-bias imputed by the clinicians and scientists and thereby improve the chances of identifying a number of similar asthma cases identified by hitherto unknown characteristics.

The first classical dichotomous phenotypes were allergic *versus* nonallergic asthma. Later, four time-based, epidemiologically observed ''wheezing'' asthma phenotypes (transient, early onset, persistent and late onset) were proposed by the Tucson Children's Respiratory Study (TCRS), which studied infants from Tucson (Arizona, TX, USA) [8]. This was later followed-up by more recent, larger, birth cohort studies. In a recent collaborative study of the two birth cohorts Prevention and Incidence of Asthma and Mite Allergy (PIAMA) and Avon Longitudinal Study of Parents and Children (ALSPAC), remarkably similar clusters of five and six phenotypes, respectively, were identified, based upon the temporal pattern of reported wheezing [9]. These represented, in the ALSPAC study ''never/infrequent'' (59%), ''transient early'' (16%), ''prolonged early'' (9%), ''intermediate'' (3%), ''late'' (16%), and ''persistent'' (7%) wheeze determined in approximately 110,000 children [10], with similar objective correlates of asthma, atopy and lung function in accordance with the five-class model from the PIAMA study [9]. However, these ''wheeze'' phenotypes are not equivalent to asthma phenotypes, although ''asthma'' was more commonly defined in the intermediate, late and persistent wheezing phenotypes.

A recently published PRACTALL (PRACtical ALLergy) consensus reported criteria for defining asthma endotypes on the basis of their phenotypes and putative pathophysiology [11]. Some examples of phenotypes listed were eosinophilic asthma, exacerbation-prone asthma, obesity-related asthma, exercise-induced asthma (EIA), adult-onset asthma, fixed airflow limitation and poorly steroid-responsive asthma. However, they only partly overlap with the suggested endotypes, which were aspirin-sensitive asthma, allergic bronchopulmonary mycosis (ABPM), allergic asthma (adults), asthma predictive index (API) [12], positive preschool wheezer, severe late-onset hypereosinophilic asthma and asthma in cross-country skiers [11]. It is unclear if this relabelling will improve our current understanding of the underlying mechanisms and lead to a more targeted drug development.

Asthma as an allergic disease

There is no doubt that asthma is associated with allergic sensitisation [13–15], but with a significant variability in the strength of association between atopic sensitisation and asthma [16]. The fraction of wheeze attributable to atopy varies markedly, ranging from 0% in Turkey to 94% in China [16], as does the presence of allergic sensitisation in school-aged asthmatics (from 55–60% in Scandinavia [17, 18] and 95% in Australia [19]). Asthma has thus been regarded, predominantly, as an allergic disease. Furthermore, it is considered one of the clinical diseases expressed in a predominant temporal pattern within the ''atopic'' or ''allergic march'' from atopic dermatitis to allergic rhinitis and asthma [20, 21]. There is an emerging focus on the different asthma phenotypes throughout life, which are based upon observable traits, *e.g.* asthma with and without allergic sensitisation, eosinophilic or non-eosinophilic inflammation dominating the biopsy specimens [22, 23], and heterogeneity in response to treatment [24, 25]. This is seen in the context of trying to identify ''atopic'' genotypes to correlate with the asthma presentation; hitherto a relatively unsuccessful exercise.

Another issue of asthma as an allergic disease is that it is not clear to what extent eosinophilic inflammation is systemic or predominantly local [26]. Furthermore, most atopic subjects (*i.e.* those producing immunoglobulin (Ig)E antibodies towards common inhalant and food allergens) do not have asthma, and asthma-like clinical presentations (often referred to as "wheezy" disorders in children) are common prior to any signs or documentation of allergic markers [27].

Asthma in early childhood is difficult to diagnose, probably more so than in later childhood or in adults [28]. The clinical presentation of asthma varies throughout childhood, and the concept of diagnosing "asthma" distinct from other wheezy asthma-like presentations or phenotypes in early childhood is a debatable topic [29, 30]. One of the most problematic areas of understanding childhood asthma is probably related to "wheezy" disorders in the first few years of life. On one hand, asthma often debuts as wheezing within the first few years of life, on the other hand wheeze often appears early without clear signs of developing into asthma later in life.

The concept of phenotypes suggests a link to specific genotypes, whereby one individual should be distinguished from another by these characteristics. Clearly, this is not the case today for childhood asthma [1, 11, 31].

Is EIA a distinct phenotype?

EIA is common and sometimes the only manifestation of asthma in children and adolescents. Some 30 years ago it was stated that EIA occurred in 70–80% of asthmatic children that had not been treated with inhaled steroids, but this has been difficult to confirm in population studies [32]. Rather, in 10-year old children, exercise-induced bronchoconstriction (EIB) has been reported in approximately 8% of the normal population compared with almost 37% in the current asthma population [17]. Furthermore, many top performing athletes develop asthma and the mechanisms of their bronchial hyperresponsiveness (BHR) may differ from asthma presenting in early life. EIA is thought to be due to increased ventilation, caused by an increased in demand for oxygen, which is related to physical exercise through water loss and cooling of the airways. The cooling airways give rise to reflex parasympathetic nerve stimulation that results in bronchoconstriction [33–35]. Alternatively, water loss from the bronchial mucosa induces movement of water from inside the cell to the extracellular space [36], causing an intracellular increase in ion concentration [37] that possibly leads to mediator release mediators [36]. The possible epithelial barrier damage caused by extreme exercise may thus represent a specific phenotype, but this remains to be proven by further studies [38].

Classical phenotypes

The classical approach to childhood asthma has been to define asthma by various diagnostic criteria, and to add different allergic or atopic features to try and separate sub-groups of asthma. Thus, traits commonly appearing with, but not limited to, asthma (such as BHR or atopic sensitisation) are often added to "asthma" in order to try to distinguish one group of asthma from another. This may not be an optimal approach. There is a lack of common agreement for the diagnostic criteria of asthma to include all asthma and exclude all without asthma [28, 39–41]. The pragmatic asthma definitions, thereby, reflect a variety of asthma outcomes. The term "wheeze" is particularly problematic as it is not relevant to non-English speaking parts of the world. This symptom and sign of bronchial obstruction is a hallmark of early asthma, but may also have other pathophysiologic origins. A single episode, or few episodes, of wheeze is common in the first 1–2 years of life, usually occurring with a lower respiratory tract infection (LRTI), which often respond poorly to anti-asthmatic treatment [42, 43]; however, the wheeze is reportedly resolved in more than half of the children reported to have wheezed [29]. Although the term appears useful for objective correlates in many studies [9, 29, 44], it appears less useful in others [17, 45, 46]. However, the likelihood of asthma later in childhood increases with the number and severity of bronchiolitis obliterans (BO) episodes in the first few years of life [47], although predicting asthma

even by the presence of early BO, IgE antibodies or other atopy-related characteristics are difficult [48, 49].

Most asthma studies combine the presence of symptoms and reversible airflow obstruction, as well as a doctor's diagnosis of asthma, in their asthma definitions. However, a wide range of features have been proposed to subclassify asthma. These include: asthma symptoms, exacerbations, response to treatment, lung function, BHR, allergic sensitisation, allergic comorbidities, and triggers, as well as varying markers of inflammation [6, 10, 50, 51]. Adding markers of inflammation is probably necessary [7, 52], but has not yet proved valuable in subdividing classical phenotypes of childhood asthma. This may, in part, be because local inflammatory changes are less easily studied with the lack of local biological specimens. An obvious challenge in adding inflammatory and immunological markers to clinical characteristics is that very few subjects will eventually be classified within each phenotype. The likelihood of statistical power to detect meaningful risk factors and biological correlates is thereby reduced [6].

Development of approaches to define asthma phenotypes

Moving from the classical, clinically based phenotypes, the study undertaken on the infants in the TCRS study [8, 53] suggested that classification by temporal clinical presentation, when combined with allergic sensitisation, could propose phenotypes with potentially different underlying mechanisms as well as prognosis [8, 54]. This approach was later followed by more advanced statistical approaches to cluster groups of children with similar characteristics. One of these methods is latent class analysis [9, 10]. Although less biased than by a priori group comparisons performed by the researchers, a shortcoming is that the outcome was based upon "did the child wheeze within the last year". The (temporal) variable "wheeze" in the latest period resulted in remarkable similarities between the six ("never/infrequent", "transient early", "prolonged early", "intermediate", "late", and "persistent" wheeze) and five classes identified in the ALSPAC study and PIAMA study, respectively, as well as their correlates with traits such as allergic sensitisation, lung function and asthma [9].

Despite an improvement from researcher-driven hypotheses, there are, nevertheless, disadvantages to such an approach. Since the phenotypes are by nature retrospective, they are not helpful for the clinician. The time-points of definition are arbitrary, depending upon the time of follow-up investigations rather than biologically relevant events. The strength of interaction with risk factors may change and gene–environmental interactions are not accounted for [55]. The approach does not account for complex associations and interactions between the varying spectrums of factors likely to be involved in phenotype characteristics [6, 7, 9, 11, 56].

To reduce some of these shortcomings, SMITH *et al.* [57] described the use of data driven principal component analyses in a population-based cohort to identify groups of children with similar characteristics. Data from interviews, lung function (specific airway resistance), atopy and BHR at 3 and 5 years were used and five-group variants (components) were identified: wheeze, wheeze with irritants, wheeze with allergens, cough, and chest congestion with correlates to atopy and BHR.

A limitation with many of the approaches is the fact that most of the traits determining underlying pathophysiology are likely to be quantitative, rather than qualitative [58, 59]. This was shown by the quantitative measures of obstructive airways disease and specific IgE at 2 years being better predictors for later asthma than did the mere presence of these traits [48, 59].

Mathematical techniques, such as latent class analysis [10], principal component analysis [57], and de-trended fluctuation analysis (DFA) [60] have all been applied in asthma phenotyping and to identify children at risk for exacerbations [60]. Unsupervised cluster analyses were also used to identify severe childhood asthma phenotypes in a Paris (France) cohort [61]. Two distinct clusters of severe asthma were described. The "asthma with severe exacerbations and multiple allergies" cluster was characterised by more food allergies, more blood eosinophils, more basophils, more

uncontrolled asthma despite higher doses of inhaled corticosteroid, and an increase in hospitalisations. The second cluster "severe asthma with bronchial obstruction" represented older children with higher body mass index (BMI), lower lung function, more pronounced blood neutrophils and higher levels of all classes of immunoglobulin, apart from IgE [61]. A third cluster of mild asthma did not have distinct characteristics [61].

Rather than determining specific asthma phenotypes, it is increasingly likely that an approach identifying intermediate phenotypes may be of value. Thus, objective measures can be tested against clinical traits, as well as genotypes and gene–environment interactions [7, 62–65]. In the American Severe Asthma Research Program (SARP), intermediate phenotypes and various statistical models were used to identify predictors of bronchoalveolar lavage (BAL) cytokines for severe asthma [62]. This proof of principle study, to identify multidimensional BAL cytokine profiles, used intermediate quantitative asthma phenotypes in adults (determined by extreme values of BAL eosinophils and neutrophils, bronchodilator response and BHR), to test five different statistical prediction models. Their data suggested that logistic regression and multivariate adaptive regression splines produced the best methods to predict asthma phenotypes.

The optimal statistical approaches to identify the underlying pathophysiology in different phenotypes are not clear. New approaches like the integrative systems biology strategy rely on the applications of "omics" techniques (proteomics, metabolomics) with high-throughput measurement platforms integrated with biological and clinical data. These approaches may untangle phenotypic characteristics, reflecting underlying pathological mechanisms. Such understanding is essential in order to develop new biomarkers for early diagnosis, define phenotypes and disease severity, as well as predict response to therapy or drug toxicity [7]. Further studies are necessary to evaluate the application of these new tools to characterise and monitor the dynamic and complex nature of asthma.

Phenotypes and risk factors

An important feature of phenotype description is to identify relevant risk factors. The contradicting results found for the role of pet exposure and asthma, as well as other allergic diseases, may stem from our inability to distinguish relevant phenotypes [66]. Thus, such exposure may have an impact on a few subjects with certain genotype–phenotype characteristics compared with the (possible many) phenotypes, where pets do not matter. Other risk factors appear to exert a differential impact depending on when the outcome is determined; such as exposure to tobacco smoke, parental atopic disease, house dampness or reduced ventilation, allergic sensitisation, time of food allergen introduction and breastfeeding, to mention only a few. In the German Multicentre Asthma Study (MAS), it was found that the associations between risk factor (exposure) and wheeze or asthma were much stronger in early, rather than later, childhood [55]. This again raises the question as to whether or not phenotypes are stable or are altered over time. If the latter is true, then when and what are the underlying mechanisms that differentiate the changes in phenotypic expression?

Using new phenotypes in management approaches

Most recent guidelines suggest some sort of phenotypic classification to guide initial treatment [28, 43, 67, 68], stressing the need for a re-evaluation to assess treatment effect. However, trying to distinguish childhood asthma subgroups by symptoms, comorbidities, inflammatory markers, response to treatment or other features have, so far, not been very useful in the clinical settings [69]. In the search for individualised treatments, novel treatments are likely to depend upon our identification of relevant phenotypes.

Primary prevention of atopic diseases, which include asthma, has been remarkably unsuccessful so far. One aspect of this is our inability, with any level of certainty [70], in early childhood to

predict later childhood asthma [29. 47] or in childhood predict adult asthma [71]. Another aspect is to identify relevant-risk populations at an appropriate time when prevention is possible [70]. Childhood and even intra-uterine life [72, 73] represent a period in life in which immunology and pathophysiology undergoes decisive changes with life-long consequences [74, 75]. Thus, exposure to risk factors at certain time-points may differentially influence the developmental path [76]. This indicates that asthma-related outcomes may vary, not only according to early immunological and pathophysiological patterns, but may change course over time. The challenge is, therefore, to study if primary prevention of one ''atopic'' phenotype may reduce the development of another. For instance, loss-of-function in the filaggrin gene is involved in skin barrier defect and increases the risk of atopic eczema as well as asthma [77, 78]. Thus, if this triad constitutes a phenotype, is the asthma conferred through allergic sensitisation started off by allergens penetrating damaged skin? And what is the role of environmental exposure, in terms of asthma development, in the various phenotypes?

The numerous papers discussing asthma phenotypes, and the large number of suggested phenotypes (or even endotypes), are at present confusing. The overlap between the (novel) clusters (phenotypes) is often vast. No single phenotype, particularly in childhood, has, at present, significantly contributed to the individualised, targeted treatment or effective preventative strategies. Nevertheless, we need to improve our current understanding of the underlying mechanisms involved, in order to develop new drugs. And we may have to stratify primary or secondary preventive interventions in the future, based upon risk assessments and phenotypic characteristics at the start of life. But we are clearly not there at the moment.

Conclusions

Identification of ''true'' phenotypes for childhood asthma is likely to improve our understanding of the pathophysiology, increase our ability to find new treatment targets and enable us to individualise a patient's therapy. Thus, phenotype identification is likely to help us in the optimal secondary and tertiary prevention of asthma and other atopic disease; however, at present it is less likely to be useful for primary prevention. Novel data-driven statistical approaches could be essential in ascertaining the role of proteomics and with identifying new therapeutic targets, but are presently of limited usefulness for the clinician in preventing, predicting or treating childhood asthma.

Support Statement

K.C. Lødrup Carlsen is part of the MeDALL project.

Statement of Interest

One of K.C. Lødrup Carlsen's research projects, the ECA Study, has received funding from Phadia, as they supplied reagents for IgE measurements. She has also received a fee for giving a general talk on paediatric asthma from GSK. K-H. Carlsen has received fees for giving presentations from Nycomed Pharma, URIACH, MSD, Novartis. He has also received fees for consulting from MSD. These companies will not gain or lose from the present article.

References

1. Aas K. Heterogeneity of childhood asthma. *Allergy* 1981; 36: 3–14.
2. Sly PD, Boner AL, Björksten B, *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; 372: 1100–1106.
3. Silverman M, Wilson N. Wheezing phenotypes in childhood. *Thorax* 1997; 52: 936–937.
4. Martinez FD, Helms PJ. Types of asthma and wheezing. *Eur Respir J* 1998; 12: Suppl. 27, 3s–8s.
5. Sheth KK, Lemanske RF Jr. Pathogenesis of asthma. *Pediatrician* 1991; 18: 257–268.
6. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clin Exp Allergy* 2010; 40: 1130–1141.

7. Bousquet J, Anto J, Auffray C, *et al.* MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine. *Allergy* 2011; 66: 596–604.
8. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133–138.
9. Savenije OE, Granell R, Caudri D, *et al.* Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011; 127: 1505–1512.
10. Henderson J, Granell R, Heron J, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63: 974–980.
11. Lotvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
12. Taussig LM, Wright AL, Holberg CJ, *et al.* Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003; 111: 661–675.
13. Simpson BM, Custovic A, Simpson A, *et al.* NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin Exp Allergy* 2001; 31: 391–399.
14. Addo-Yobo EO, Custovic A, Taggart SC, *et al.* Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol* 2001; 108: 363–368.
15. Al-Mousawi MS, Lovel H, Behbehani N, *et al.* Asthma and sensitization in a community with low indoor allergen levels and low pet-keeping frequency. *J Allergy Clin Immunol* 2004; 114: 1389–1394.
16. Weinmayr G, Weiland SK, Bjorksten B, *et al.* Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007; 176: 565–574.
17. Lødrup Carlsen KC, Håland G, Devulapalli CS, *et al.* Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; 61: 454–460.
18. Thomsen SF, Ulrik CS, Larsen K, *et al.* Change in prevalence of asthma in Danish children and adolescents. *Ann Allergy Asthma Immunol* 2004; 92: 506–511.
19. Joseph-Bowen J, de Klerk N, Holt PG, *et al.* Relationship of asthma, atopy, and bronchial responsiveness to serum eosinophil cationic proteins in early childhood. *J Allergy Clin Immunol* 2004; 114: 1040–1045.
20. Illi S, von Mutius E, Lau S, *et al.* The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113: 925–931.
21. Ker J, Hartert TV. The atopic march: what's the evidence? *Ann Allergy Asthma Immunol* 2009; 103: 282–289.
22. Saglani S, Bush A. Asthma, atopy, and airway inflammation: what does it mean in practice? *Am J Respir Crit Care Med* 2008; 178: 437–438.
23. Saglani S, Bush A. The early-life origins of asthma. *Curr Opin Allergy Clin Immunol* 2007; 7: 83–90.
24. Szefler SJ, Martin RJ, King TS, *et al.* Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002; 109: 410–418.
25. Szefler SJ, Phillips BR, Martinez FD, *et al.* Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005; 115: 233–242.
26. Ozdemir C, Akdis M, Akdis CA. T-cell response to allergens. *Chem Immunol Allergy* 2010; 95: 22–44.
27. Custovic A, Taggart SC, Woodcock A. House dust mite and cat allergen in different indoor environments. *Clin Exp Allergy* 1994; 24: 1164–1168.
28. Bacharier LB, Boner A, Carlsen KH, *et al.* Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63: 5–34.
29. Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma. *Curr Opin Allergy Clin Immunol* 2011; 11: 157–161.
30. von Mutius E. Trajectories of childhood wheeze. *J Allergy Clin Immunol* 2011; 127: 1513–1514.
31. Bousquet J, Burney PG, Zuberbier T, *et al.* GA(2)LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma ''epidemic''. *Allergy* 2009; 64: 969–977.
32. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise-induced asthma. *Thorax* 1985; 40: 481–487.
33. Carlsen KH, Anderson SD, Bjermer L, *et al.* Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008; 63: 387–403.
34. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, *et al.* Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979; 46: 467–475.
35. McFadden ER Jr, Nelson JA, Skowronski ME, *et al.* Thermally induced asthma and airway drying. *Am J Respir Crit Care Med* 1999; 160: 221–226.
36. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is… *J Allergy ClinImmunol* 2000; 106: 453–459.
37. Eveloff JL, Warnock DG. Activation of ion transport systems during cell volume regulation. *Am J Physiol* 1987; 252: F1–F10.
38. Bougault V, Turmel J, St-Laurent J, *et al.* Asthma, airway inflammation and epithelial damage in swimmers and cold-air athletes. *Eur Respir J* 2009; 33: 740–746.
39. Baena-Cagnani CE, Badellino HA. Diagnosis of allergy and asthma in childhood. *Curr Allergy Asthma Rep* 2011; 11: 71–77.

40. Pedersen SE, Hurd SS, Lemanske RF Jr, *et al.* Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol* 2011; 46: 1–17.
41. Horner CC, Bacharier LB. Diagnosis and management of asthma in preschool and school-age children: focus on the 2007 NAEPP Guidelines. *Curr Opin Pulm Med* 2009; 15: 52–56.
42. Boehmer AL. Paediatric asthma: everything that seemed to be certain no longer is. *Paediatr Respir Rev* 2010; 11: 185–190.
43. Frey U, von Mutius E. The challenge of managing wheezing in infants. *N Engl J Med* 2009; 360: 2130–2133.
44. Custovic A, Söderström L, Ahlstedt S, *et al.* Allergen-specific IgG antibody levels modify the relationship between allergen-specific IgE and wheezing in childhood. *J Allergy Clin Immunol* 2011; 127: 1480–1485.
45. Mellis C. Respiratory noises: how useful are they clinically? *Pediatr Clin North Am* 2009; 56: 1–17.
46. Van Sickle D. Perceptions of asthma among physicians: an exploratory study with the ISAAC video. *Eur Respir J* 2005; 26: 829–834.
47. Devulapalli CS, Carlsen KC, Haland G, *et al.* Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008; 63: 8–13.
48. Lødrup Carlsen KC, Söderström L, Mowinckel P, *et al.* Asthma prediction in school children; the value of combined IgE-antibodies and obstructive airways disease severity score. *Allergy* 2010; 65: 1134–1140.
49. Leonardi NA, Spycher BD, Strippoli MP, *et al.* Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011; 127: 1466–1472.
50. Fitzpatrick AM, Higgins M, Holguin F, *et al.* The molecular phenotype of severe asthma in children. *J Allergy Clin Immunol* 2010; 125: 851–857.
51. Fitzpatrick AM, Teague WG, Meyers DA, *et al.* Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011; 127: 382–389.
52. Hollams EM, Deverell M, Serralha M, *et al.* Elucidation of asthma phenotypes in atopic teenagers through parallel immunophenotypic and clinical profiling. *J Allergy Clin Immunol* 2009; 124: 463–470.
53. Martinez FD, Morgan WJ, Wright AL, *et al.* Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. *Am Rev Respir Dis* 1991; 143: 312–316.
54. Silverman M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. *Thorax* 1993; 48: 1200–1204.
55. Matricardi PM, Illi S, Grüber C, *et al.* Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008; 32: 585–592.
56. Holgate ST, Arshad HS, Roberts GC, *et al.* A new look at the pathogenesis of asthma. *Clin Sci (Lond)* 2010; 118: 439–450.
57. Smith JA, Drake R, Simpson A, *et al.* Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008; 177: 1358–1363.
58. Castro-Rodriguez JA, Cifuentes L, Rodríguez-Martínez CE. The asthma predictive index remains a useful tool to predict asthma in young children with recurrent wheeze in clinical practice. *J Allergy Clin Immunol* 2011; 127: 1082–1083.
59. Simpson A, Söderström L, Ahlstedt S, *et al.* IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol* 2005; 116: 744–749.
60. Stern G, de Jongste J, van der Valk R, *et al.* Fluctuation phenotyping based on daily fraction of exhaled nitric oxide values in asthmatic children. *J Allergy Clin Immunol* 2011; 128: 293–300.
61. Just J, Gouvis-Echraghi R, Rouve S, *et al.* Two novel severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J* 2012; [Epub ahead of print DOI: 10.1183/09031936.00123411].
62. Brasier AR, Victor S, Ju H, *et al.* Predicting intermediate phenotypes in asthma using bronchoalveolar lavage-derived cytokines. *Clin Transl Sci* 2010; 3: 147–157.
63. Torjussen TM, Lødrup Carlsen KC, Munthe-Kaas MC, *et al.* Alpha-nicotinic acetylcholine receptor and tobacco smoke exposure: effects on bronchial hyperresponsiveness in children. *Pediatr Allergy Immunol* 2012; 23: 40–49.
64. Custovic A, Rothers J, Stern D, *et al.* Effect of day care attendance on sensitization and atopic wheezing differs by Toll-like receptor 2 genotype in 2 population-based birth cohort studies. *J Allergy Clin Immunol* 2011; 127: 390–397.
65. Zhao L, Bracken MB. Association of CD14 -260 (-159) C>T and asthma: a systematic review and meta-analysis. *BMC Med Genet* 2011; 12: 93.
66. Takkouche B, Gonzalez-Barcala FJ, Etminan M, *et al.* Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy* 2008; 63: 857–864.
67. Levy ML, Thomas M, Small I, *et al.* Summary of the 2008 BTS/SIGN British Guideline on the management of asthma. *Prim Care Respir J* 2009; 18: Suppl. 1, S1–S16.
68. Cope SF, Ungar WJ, Glazier RH. International differences in asthma guidelines for children. *Int Arch Allergy Immunol* 2009; 148: 265–278.
69. Lemanske RF Jr, Mauger DT, Sorkness CA, *et al.* Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010; 362: 975–985.

70. Lødrup Carlsen KC, Mowinckel P, Granum B, *et al.* Can childhood asthma be predicted at birth? *Clin Exp Allergy* 2010; 40: 1767–1775.
71. Balemans WA, van der Ent CK, Schilder AG, *et al.* Prediction of asthma in young adults using childhood characteristics: development of a prediction rule. *J Clin Epidemiol* 2006; 59: 1207–1212.
72. Breckler LA, Hale J, Jung W, *et al.* Modulation of *in vivo* and *in vitro* cytokine production over the course of pregnancy in allergic and non-allergic mothers. *Pediatr Allergy Immunol* 2010; 21: 14–21.
73. Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions *in utero*. *Curr Opin Allergy Clin Immunol* 2009; 9: 417–426.
74. Blume C, Foerster S, Gilles S, *et al.* Human epithelial cells of the respiratory tract and the skin differentially internalize grass pollen allergens. *J Invest Dermatol* 2009; 129: 1935–1944.
75. Landau LI. Definitions and early natural history. *Med J Aust* 2002; 177: Suppl., S38–S39.
76. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009; 6: 272–277.
77. Marenholz I, Kerscher T, Bauerfeind A, *et al.* An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol* 2009; 123: 911–916.
78. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38: 441–446.

Chapter 2

Infantile and preschool asthma

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SUMMARY: In infants and preschool children the symptoms suggestive of asthma (*e.g.* wheeze) may be a clinical expression of a number of diseases with different aetiologies. If this is true, then it is unlikely that these different diseases would respond to the same treatment. Consequently, implementation of a management strategy which is effective for each individual patient is challenging, and controversies remain with respect to which patients should be given anti-asthma treatment, and when the treatment should be started and for how long. Whilst acknowledging these uncertainties, practicing physicians may use the Asthma Predictive Index (API) as a guide in clinical practice to identify young children with recurrent wheezing who are at risk of the subsequent development of persistent asthma, and who may benefit from preventative anti-asthma medication. We acknowledge that a number of questions on the most appropriate management strategy remain unanswered, including which type of medication is the best for individual patients (*e.g.* short-acting β-agonist *versus* inhaled corticosteroid (ICS) *versus* leukotriene receptor antagonist (LTRA)), dose (high *versus* low) and schedule (regular *versus* as needed).

KEYWORDS: Asthma, infants, predictive index, preschoolers, treatment, wheezing

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Even though almost 80% of asthmatics start having symptoms during the first 5 years of their life, asthma diagnosis in infants and preschool-aged (preschoolers) children is more challenging than in older children and adults [1]. Recurrent wheezing is frequently reported in preschoolers and is often association with upper respiratory tract infections (URTI), which in this age group occurs approximately six to eight times per year [2]; however, for many of these children wheezing does not recur later in life [3]. An additional challenge in this age group is that clinicians and practitioners often rely on parentally reported wheezing, which may be unreliable [4]. Furthermore, other conditions give rise to snoring, upper airway secretions, rattling sounds reflective of airway secretions or noisy breathing, all of which could be misinterpreted as a wheeze [5], and conventional pulmonary function testing is unavailable in most medical centres for children under the age of 5 years. Preschoolers are often diagnosed with asthma when a cough with wheezing or dyspnoea, which fluctuates over time, is reported in combination with the findings from a physical exam, family history and the presence of other clinical atopic diseases,

such as eczema or allergic rhinitis; response to treatment (either bronchodilator or continuously administered anti-inflammatory therapy) is also taken into account [6].

Phenotypes

Preschool wheezing is a highly heterogeneous condition and several birth cohort studies have proposed different phenotypes of childhood wheezing, based on its natural history [7]. The identification of the different phenotypes is important for studying the developmental pathways of asthma and the underlying disease mechanisms involved, the decision making process with regards the most appropriate treatment and the prediction of the clinical evolution [8]. A classic example of phenotyping, based on the temporal pattern of wheezing, was described in the well-known Tucson Children's Respiratory Study (TCRS), which identified three phenotypes based on the moment of onset and the resolution of wheezing. Symptoms with onset before 3 years of age were termed transient or persistent, depending on whether they had been resolved by the age of 6 years, while late-onset wheeze referred to symptoms that commenced after the age of 3 years and persisted thereafter [3]. This and other studies have suggested children with transient wheezing usually have no symptoms between colds and that this phenotype is related to a decreased lung function at birth, maternal smoking during pregnancy [9], male sex, presence of older siblings, attendance at a nursery [10–12], and the absence of atopy [13]. Alternatively, children with persistent wheezing may: have exacerbations caused by colds, allergens, or irritants; exhibit symptoms between major exacerbations; tend to have clinical atopic diseases, such as eczema or allergic rhinitis; often have first-degree relatives with atopy or asthma; and be born without any significant alteration of lung function [14]. In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study, using longitudinal latent class analysis, six different phenotypes were identified: never/infrequent wheeze, transient-early wheeze, prolonged-early wheeze, intermediate-onset wheeze, late-onset wheeze, and persistent wheeze [15]. A recent cross-cohort comparison of modelled phenotypes between ALSPAC and Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohorts has suggested that wheezing phenotypes identified by longitudinal latent class analysis were comparable in these births cohorts [16].

Recently, several publications have demonstrated the utility of an unbiased clustering approach in multidimensional data to identify different phenotypes of preschool asthma. In the Leicester cohort study, using a cluster analysis, three distinct wheeze phenotypes were identified: atopic persistent wheeze (patients with reduced levels of lung function and greater levels of bronchial hyperreactivity compared with healthy children), non-atopic persistent wheeze (patients who wheezed more commonly in winter and who were rarely atopic), and transient viral wheeze (patients with infrequent wheeze episodes triggered mostly by colds, which was resolved 2 to 4 years after the first survey) [17]. A principle component analysis using answers to multiple questions relating to wheeze and cough in Manchester Asthma and Allergy Study (MAAS) identified five distinct clinical phenotypes of coexisting symptoms amongst preschool children by the age of 5 years [18]. Similar phenotypic heterogeneity has been suggested for other secondary phenotypes often associated with preschool asthma (*e.g.* atopy) [19].

Although this body of work has improved the current understanding of the mechanisms and natural history of preschool wheezing disorders, the risk factors for the persistence and relapse of childhood asthma, as well as the outcome of pulmonary function, the phenotype allocation is very difficult (if not impossible) in a real-life clinical situation when a practicing paediatrician is assessing a young child with recurrent wheezing. Therefore, different wheeze phenotypes derived from the birth cohort studies are not particularly helpful for the management of patients in clinical practice [20]. Hence, a symptom-based classification has recently been proposed by the European Respiratory Society (ERS) Task Force on preschool wheeze as a treatment guide for clinicians in their everyday practice and for use in interventional studies that divide wheezing illnesses in preschool children into episodic (viral) wheeze (EVW) and multiple-trigger wheeze (MTW) phenotypes [21]. According to this classification, the term EVW refers to children with

exacerbations exclusively triggered by viral respiratory infections with no symptoms between episodes. Conversely, the term MTW refers to children who wheeze in response not only to viruses but also to other triggers, such as allergens, activity, weather, or cigarette smoke [21]. This has been considered a pragmatic and useful classification for preschoolers with recurrent wheezing, for everyday clinical practice, because some investigators believe it to be an important determinant of response to treatment: maintenance treatment with low to moderate continuous inhaled corticosteroids (ICS) is considered ineffective in patients with EVW [22, 23], while ICS maintenance works in patients with MTW [24]. Conversely, maintenance in addition to intermittent therapy with montelukast [25], as well as episodic high doses of ICS [22, 26], has a role in children with EVW. However, the proposed EVW/MTW classification has been recently criticised for several reasons. First, there is little evidence that these phenotypes are related to the longitudinal patterns of wheeze, or to different pathological processes [8]. Secondly, this symptom pattern of wheeze has not been objectively validated by pulmonary function tests or markers of airway inflammation, therefore, it is not clear if EVW and MTW represent distinct conditions with unique pathogenic mechanisms or are simply severity markers of the same disease [27]; however, SONNAPPA *et al.* [28] demonstrated lower levels of conductive airway ventilation inhomogeneity in patients that exhibit the MTW phenotype compared with EVW. Thirdly, this classification does not allow for differentiation between occurrences of wheeze of distinct severity and frequency from other respiratory symptoms, such as cough, colds, and chest congestion, and this is not taken into consideration [8]. Lastly, these two phenotypes do not appear to be stable over time; SCHULTZ *et al.* [29] recently demonstrated that children frequently change from exhibiting one type of clinically defined wheeze to the other in a course of only 1 year. Therefore, there is limited evidence to support the EVW/MTW classification and it is likely to change when additional evidence becomes available.

Prediction of wheeze persistence (clinical risk of asthma indices)

Identification of symptomatic preschoolers with recurrent wheezing who will go on to develop asthma enables an improvement in targeting secondary preventive actions and therapeutic strategies for those who are most likely to benefit [30]. To help in the early identification of preschoolers who wheeze and are at high risk of developing persistent asthma symptoms, a number of asthma predictive scores have been reported. By far the most widely used of these scores, in both the clinical and the research context, is the Asthma Predictive Index (API), developed about 10 years ago by using data from 1,246 children in the TCRS birth cohort [13]. This score combines simple and easily measurable clinical and laboratory parameters that can be obtained in any clinical setting. A positive API score requires recurrent episodes of wheezing during the first 3 years of life, as well as either one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia greater than 4%). A loose index (fewer than three episodes per year and either one of the major or two of the minor criteria) and a stringent index (greater than three episodes per year and one of the major or two of the minor criteria) were created. Upon applying this algorithm, in the TCRS, children with a positive API were 2.6–13 times more likely to have active asthma between the ages of 6 and 13 years when compared with children who had a negative API [13]. A modified API (mAPI), which was used in a randomised trial of 285 subjects, incorporated allergic sensitisation to one or more aeroallergens as a major criterion and allergic sensitivity to milk, eggs or peanuts as a minor criterion, replacing physician-diagnosed allergic rhinitis in the original API [31].

Since the API was developed, some other asthma predictive scores have been devised, all including different factors predictive of wheeze persistence. In 2003, KURUKULAARATCHY *et al.* [32] developed a scoring system using data from 1,456 children in the Isle of Wight birth cohort. They found that a positive family history of asthma, a positive allergy skin-prick test at 4 years of age and recurrent chest infections at 2 years of age were associated with an increased risk of asthma at the age of 10 years [32]. More recently, in 2009 CAUDRI *et al.* [33], using data from 3,963 children from the

PIAMA birth cohort in the Netherlands, developed a predictive score called the PIAMA risk score, based on eight easily discernible clinical parameters (male sex, post-term delivery, parental education, inhaled medication used by parents, wheezing frequency, wheezing/dyspnoea apart from colds, number of respiratory tract infections, and diagnosis of eczema). Upon applying this predictive score to this birth cohort, children scoring 30 or higher had a risk factor >40% of having asthma at the age of 7–8 years [33].

Asthma predictive indices, especially the API, have been criticised because: they have been applied in clinical practice without a formal validation process having been performed in different populations *i.e.* external validation; they are not useful in predicting the long-term prognosis of preschool children with more severe or recurrent wheeze in clinical practice [34]; and they are relatively complex, whilst having no substantial benefit for predicting later asthma when compared with other simple prediction rules based on only frequency of wheeze [35]. However, those criticisms are not scientifically justifiable [36]. For example, the API and the PIAMA risk scores have recently been validated in independent populations [30, 35], and the API is an especially popular clinical prediction rule that combines simple and easily measurable clinical and laboratory parameters [13, 37] and that has been used for various purposes, such as recruiting children with high risk of developing persistent asthma symptoms for clinical trials [38, 39] and as a guide for treatment of preschoolers with recurrent wheezing in clinical practice [37]. The API was adopted in the most well-known asthma guidelines, Global Initiative for Asthma (GINA) [40] and National Institutes of Health (NIH) [41]. Finally, it is important to remark that the best parameter for determining the utility of any diagnostic test is the likelihood ratio, which in the case of the API is 7.3. This means that in places with a population at low, moderate, or high risk of having asthma at school age, *e.g.* 10%, 20% or 40%, for a child that goes to a paediatric clinic for recurrent wheezing episodes, the use of the API increases the probability of a prediction of asthma by four, three or two times, respectively (*e.g.* the pre-test probability of asthma moves from 10% to 42%, from 20% to 62%, or from 40% to 80%, respectively) (fig. 1). Additionally, the most useful property of the API is its ability to estimate the likelihood that preschoolers with recurrent wheezing will develop asthma by school age [42]. Therefore, we would argue that the use of the API and other asthma predictive scores are helpful in clinical situations and may help decrease morbidity in preschoolers with recurrent wheezing and who are at high risk of developing asthma, these scores would also help avoid the prescription of controller therapies to those children who probably have transient

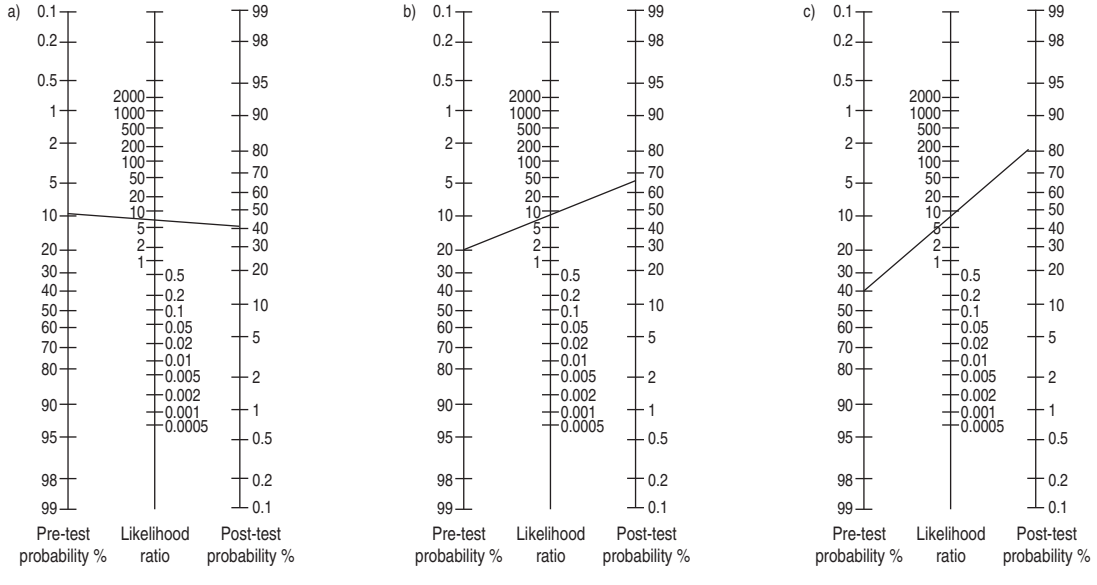

Figure 1. Application of the Asthma Predictive Index (API) at the likelihood ratio, which is 7.3, in hypothetical differing scenarios with a) a low, b) a moderate or c) a high-risk population of having asthma at school age.

wheeze rather than asthma. Moreover, there are three main reasons for diagnosing or labelling asthma in those infants/preschoolers who had recurrent wheezing and a positive API during their first 5 years of life. First, almost 80% of the asthma symptoms start during this period of life [1]. Secondly, the main decline in lung function occurs before the age of 5 years, as was shown in the TRCS [43]. Thirdly, even in developed countries the population of children with the worst asthma control is this age group [44]. Therefore, parents will be more prone to adhere to a prolonged treatment period with prevention drugs, *i.e.* ICS, if they know that the condition that causes the recurrent wheezing symptoms in their child is due to a chronic disease called asthma.

Treatment

In general, studies of therapy for preschool wheezing are often difficult to interpret, as they generally include heterogeneous groups of participants, with differences in age range, inclusion criteria, populations under study, severity of wheeze episodes, timing of initiation and form of administrating therapeutic strategies. Therefore, careful attention to all these aspects is important in the interpretation of the literature.

Short-acting β-agonists

These drugs, *i.e.* salbutamol, terbutaline, fenoterol and levalbuterol HFA, are the medications of choice to relieve bronchospasms during acute exacerbations of asthma/wheezing and for the treatment of exercise-induced bronchoconstriction (EIB). They should only be used on an as-needed basis at the lowest doses and frequency required; increased use, especially daily use, is a warning of deterioration of the disease and indicates the need to reassess treatment [40, 41].

Inhaled therapy constitutes the cornerstone of wheezing/asthma treatment in infants/preschoolers. A pressurised metered-dose inhaler (pMDI) with a valve spacer (with or without a face mask, depending on the child's age) is the preferred delivery system.

Inhaled corticosteroids

Preventing episodes of EVW have been shown to be difficult, with physicians often having no other option than to explain to parents how in a high proportion of cases the frequency and the severity of the exacerbations triggered by viral infections tend to diminish with the growth of the child [27]. Regular treatment with low-to-moderate ICS doses in children with EVW has been shown to be ineffective, and does not reduce the frequency or severity of the episodes. WILSON *et al.* [23] in a possibly underpowered study of 161 randomised patients with EVW, could not demonstrate significant differences in the use of rescue oral corticosteroids (OCS), admission to hospital, overall scores, number of symptom-free days, severity of symptoms, or duration of episodes between treatments when they compared budesonide (BD) 400 ug·day^{-1} *versus* placebo, administered over the course of a 4-month period [23]. A Cochrane review that tested if corticosteroid treatment, given episodically or daily, is beneficial to children with EVW concluded that there is no current evidence to favour maintenance, low-dose ICS for the prevention and management of episodic mild EVW [22].

In contrast, high-quality research evidence supports the use of ICS in preschoolers with MTW. BISGAARD *et al.* [45] gave either fluticasone propionate (FP) or sodium cromoglycate (SCG) for a 52-week period to a randomised group of 625 children aged from 1 to 3 years who had recurrent wheezing. Nearly half of the enrolled children had a history of atopic eczema or a family history of asthma, which is suggestive of the MTW phenotype in a great proportion of them. FP was associated with a significant reduction in symptoms, exacerbations, use of OCS and the use of rescue treatments compared with SCG [45]. WASSERMAN *et al.* [46] compared either FP twice daily *versus* placebo for 12 weeks in 332 children aged from 24 to 47 months with symptoms suggestive of MTW. When compared with placebo use FP significantly reduced asthma exacerbations, asthma symptoms and rescue albuterol use [46]. Similarly, CHAVASSE *et al.* [47] gave either FP

twice daily or a placebo during a 12-week period to a randomised group of 52 infants under the age of 1 year who had recurrent wheezing or cough and a personal or a first degree relative's history of atopy. FP was associated with significant improvement in mean daily symptoms and symptom-free days when compared with placebo treatment [47]. GUILBERT *et al.* [38] in the Prevention of Early Asthma in Kids (PEAK) study randomly assigned 285 children aged from 2 to 3 years with recurrent wheezing and a positive mAPI to treatment with either FP or a placebo for 2 years, followed by a 1-year period without medication. During the treatment period, use of FP was associated with a significantly greater proportion of episode-free days, a significant reduction in the use of rescue bronchodilators and a reduced rate of exacerbations that required the use of rescue OCS. However, there was no effect on asthma-related outcomes during the 1-year observational period after ICS was stopped, suggesting that the natural course of asthma in preschoolers, at high risk for subsequent asthma, is not modified by treatment with ICS. As a note of caution, it is important to mention that a reduction in the rate of growth was observed in the group assigned to ICS during the first year of treatment, suggesting that treatment with an ICS temporarily slows, but not progressively, the rate of growth in young children [40]. Finally, CASTRO-RODRIGUEZ and RODRIGO [48] conducted a meta-analysis on 29 randomised clinical trials (n=3,592) to compare the efficacy of ICS in infants and preschoolers with recurrent wheezing or asthma. They reported that patients who received ICS had significantly less wheezing/asthma exacerbations than those given a placebo (reduction by nearly 40% and with a number needed to treat of seven); *post hoc* subgroup analysis suggests that this effect was higher in those with a diagnosis of asthma than wheezing, but was independent of age (infants *versus* preschoolers), atopic condition, type of inhaled corticosteroid (BD *versus* FP), mode of delivery (metered-dose inhaler (MDI) *versus* nebuliser), and study quality and duration (less than 12 weeks *versus* equal to or greater than 12 weeks). In addition, children treated with ICS had significantly fewer withdrawals caused by wheezing/asthma exacerbations, reduced albuterol usage and more clinical and functional improvement than those on the placebo [48]. Consequently, regular treatment with ICS seems a reasonable strategy in children with moderate/severe recurrent wheezing, but therapy is only effective while being administered and cannot alter the natural history of the disease.

However, for young children with mild/moderate recurrent wheeze, perhaps the use of intermittent low-dose ICS with short-acting β_2-agonists (as required) will be enough, as was recently demonstrated in the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST) study by ZEIGER *et al* [49]. They showed, in a random parallel study undertaken on 278 children aged from 12 to 53 months, that BD on a regular low-dose regimen (0.5 mg per night) was not superior to an intermittent high-dose regimen (1 mg twice a day for 7 days, starting early during a predefined respiratory tract illness) in reducing asthma exacerbations; however, daily administration led to a greater exposure to the drug during the year of the study [49]. If more studies confirm this finding, maybe intermittent therapy with high-dose ICS should be enough for controlling symptoms in infants/preschoolers with recurrent wheezing, avoiding secondary effects of daily chronic ICS use. Finally, taking the experience from the recent TReating Children to Prevent Exacerbations of Asthma (TREXA) study performed on 288 schoolchildren and adolescents (aged from 5 to 18 years) [50]. It was observed that ICS, when used as a rescue medication with short-acting β_2-agonists, might be an effective step-down strategy for young children with well-controlled mild asthma. This finding needs to be replicated in infants/preschoolers. Also, trials with regular low-dose regimen *versus* intermittent low-dose ICS with short-acting β_2-agonists should be studied, since a proportion of preschoolers with mild disease are overtreated, whilst those with severe disease are undertreated [50]. Perhaps, in the future, the use of intermittent low-dose ICS with short-acting β_2-agonists (*p.r.n.*) would be a good option for those young children with mild/moderate recurrent wheeze.

Alternatively, since children with EVW have exacerbations triggered solely by viral respiratory infections with no symptoms between episodes, their parents, in part because of concerns about secondary effects, usually prefer to provide treatments intermittently rather than continuously.

Consequently, various randomised clinical trials have tested if the intermittent use of ICS is beneficial for the acute management of preschoolers with EVW. Four studies have reported improved outcomes when ICS were used acutely for the management of EVW, specifically in the reduction of symptoms and OCS uses. DUCHARME *et al.* [51] reported a 50% reduction in the need for rescue OCS and a 20% reduction in other markers of severity and duration of exacerbations, through administering FP at a dose of 1,500 $\mu g \cdot day^{-1}$ to 129 children aged from 1 to 6 years of age, beginning at the onset of a URTI and continuing for a maximum of 10 days, over a period of 6–12 months. However, treatment with FP was associated with reduced height and weight gain [51]. SVEDMYR *et al.* [52] randomly assigned 55 children aged from 1 to 3 years with EVW to receive either BD or a placebo, beginning at the first sign of a URTI and continuing for 10 days. BD was administered at 1,600 $\mu g \cdot day^{-1}$ for the first 3 days and then at 800 $\mu g \cdot day^{-1}$ for the following 7 days. Asthma symptom scores were lower in children treated with BD than in those prescribed the placebo; however, the need for hospital care was not significantly different between the two groups [52]. WILSON and SILVERMAN [26] treated 24 preschoolers with episodic asthma, who were aged between 1–5 years, with either beclomethasone dipropionate (BDP) (2,250 $\mu g \cdot day^{-1}$) or a placebo, beginning at the first sign of an asthma attack and continuing for 5 days. Both daytime and night-time symptoms over the first week of the attack were significantly reduced with BDP treatment [26]. Likewise, CONNETT and LENNEY [53] reported that both mean daytime wheeze and mean night-time wheeze in the first week after infection were significantly lower in children with EVW treated with 1,600 $\mu \cdot day^{-1}$ of BD compared with the placebo, beginning at the onset of a URTI and continuing for 7 days or until symptoms had resolved for 24 hours [26]. A Cochrane review reported a non-significant trend towards a 50% reduction in requirement for OCS with improved symptoms and parental preference, concluding that episodic high-dose ICS provide a partially effective strategy for the treatment of mild EVW in childhood [22]. Given the occurrence of an average of six to eight URTI per year in children, the high doses of ICS used in these studies, and the reduced rate of growth in height and weight reported with this strategy, the benefits of ICS must be balanced against the potential side-effects of repeated short courses of high doses of ICS. Therefore, this strategy for treating preschoolers with EVW should not be routinely recommended for use in clinical practice.

Oral corticosteroids

Since children with EVW have episodic exacerbations triggered by viral respiratory infections, various studies have evaluated if OCS when administered during the acute wheezing episodes are beneficial in these patients. The evidence for this therapeutic strategy is conflicting. CSONKA *et al.* [54] performed a randomised, placebo-controlled study on 230 children with EVW, aged between 6 and 35 months, who were attended to in an emergency room and received either oral prednisolone (2 $mg \cdot kg^{-1} \cdot day^{-1}$) or a placebo for 3 days. Although the hospitalisation rates were similar between the two groups, the severity of the disease, the length of hospital stay, and the duration of symptoms were all reduced in children treated with prednisolone [54]. Likewise, DAUGBJERG *et al.* [55] compared different treatments for acute wheezing in 123 children aged from 1.5 to 18 months, and reported a significantly earlier discharge in infants receiving prednisolone compared with those receiving terbutaline alone. In contrast to these two studies, PANICKAR *et al.* [56] in a randomised, double-blind, placebo-controlled trial, undertaken on 687 children aged from 10 to 60 months who had been admitted to three hospitals in England suffering from an attack of wheezing associated with a viral respiratory infection, evaluated the efficacy of a 5-day course of oral prednisolone (10 mg once a day for children 10 to 24 months of age and 20 mg once a day for older children). As there was no significant difference in the duration of hospitalisation, the clinical score, albuterol use, the 7-day symptom score, or the number of adverse effects, the authors concluded that in preschoolers admitted to hospital with mild-to-moderate wheezing associated with a viral respiratory infection, oral prednisolone was not superior to a placebo [56]. One other therapeutic strategy that has been considered for treating children with EVW consists of keeping the OCS at home and asking parents to commence use at the first sign of symptoms, *i.e.* without waiting for a medical review, in an effort to abort the

attack. Short courses (3–5 days) of OCS (generally prednisolone) are commonly administered in this way. OOMMEN *et al.* [57] studied 217 children aged from 1 to 5 years who had been admitted to hospital with EVW, randomising for parent-initiated prednisolone (20 mg once daily for 5 days) or a placebo for the next episode. The children were stratified for eosinophil priming. Since daytime and night-time respiratory symptom scores and the need for hospital admission did not differ between treatment groups, and no effect of eosinophil priming was observed, the authors concluded that there is no clear benefit attributable to a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years [57]. A double-blind, placebo-controlled, crossover study which enrolled children from 2 to 14 years of age for 12 months evaluated the efficacy of prednisolone (2 $mg \cdot kg^{-1}$ up to 60 $mg \cdot kg^{-1}$) administered by parents for asthma attacks that had not improved after a dose of the child's regular, acute asthma medicine. Neither the number of attacks resulting in admission nor the number of hospital days differed significantly between the two groups [58]. A Cochrane systematic review aggregated these two high-quality randomised clinical trials (303 children), and failed to find evidence that parent-initiated OCS was associated with a benefit in terms of hospital admissions, unscheduled medical reviews, symptoms scores, bronchodilator use, parent and patient impressions, physician assessment, or days lost from work or school [59]. Therefore, the authors reported that current evidence is inconclusive regarding the benefit of parent-initiated OCS in the treatment of intermittent wheezing illnesses in children, and the practice of giving parents a supply of OCS to administer to their children at the first sign of a wheezing episode should not be routinely recommended for use in clinical practice.

Montelukast

Montelukast is a leukotrine receptor antagonist (LTRA) licensed for use in children aged 6 months and older; suitable formulations (granules) are available for use in preschoolers. This medication has the advantages of oral administration and rapid action, with clinical benefit within 1 day of starting therapy, as well as a low risk of any adverse effects. Recent studies have suggested that therapy with LTRA, when administered regularly or intermittently, may be effective in children with EVW. BISGAARD *et al.* [25] in the PREvention of Viral Induced Asthma (PREVIA) study, a 12 month multicentre, double-blind, parallel-group study that enrolled 549 children aged from 2 to 5 years with a history of EVW, determined that a daily administered montelukast for a 12-month period reduced the primary end-point of the number of asthma exacerbations by approximately 32% when compared with a placebo. Montelukast was also associated with a significantly longer time to first exacerbation and reduced the overall rate of ICS usage [25]. ROBERTSON *et al.* [60] enrolled 220 children aged from 2 to 14 years with intermittent asthma and reported that parent- or caregiver-initiated episode-driven montelukast for 7 days or for 48 hours after the resolution symptoms resulted in a clinically significant reduction in healthcare resource utilisation (primary care visits and emergency department visits), missed school or work days, and improved symptom scores. However, there was no significant effect on bronchodilator or oral prednisolone use [60]. BACHARIER *et al.* [61], in the Acute Intervention Management Strategies (AIMS) study, randomised a group of 238 children aged from 12 to 59 months with EVW who had experienced at least two episodes of viral wheezing within the past year to receive one of the following for a 7-day period: episode-driven inhaled BD 1 mg twice daily plus a placebo LTRA; montelukast 4 mg once daily and placebo ICS twice daily; or placebo ICS twice daily and placebo LTRA once daily; and all in addition to albuterol. Neither the montelukast nor the inhaled BD was significantly better than the placebo when added to albuterol for the primary outcome of episode-free days over a 1-year period. However, both BD and montelukast significantly improved symptoms and activity scores. And children with positive API scores had a greater clinical benefit from both study medications than did those with negative API scores [61]. VALOVIRTA *et al.* [62] evaluated in a double-blind, double-dummy, parallel-group study, the efficacy of montelukast both daily and episode-driven for a period of 12 days beginning with signs/symptoms consistent with an imminent cold or breathing problem in children with EVW aged from 6 months to 5 years. Although, montelukast did not reduce the number of

asthma episodes culminating in an asthma attack (main outcome measure), its daily use was associated with a reduction in symptoms over the 12-day treatment period of asthma episodes, compared with the placebo, and with reduced daily and episode-driven treatment with β-agonist compared with a placebo [62]. Curiously, children with a positive API responded better to montelukast than those with a negative API. Montelukast has also been shown as an effective treatment for children with MTW. KNORR *et al.* [63] randomly assigned 689 children aged from 2 to 5 years with a history of physician-diagnosed asthma to 12 weeks of treatment with montelukast or a placebo. Montelukast produced significant improvements compared with the placebo in the following: daytime and overnight asthma symptoms, the percentage of days without asthma, the need for a rescue bronchodilator or OCS use, physician global evaluations, and peripheral blood eosinophils [63].

Only one small randomised clinical trial has compared directly ICS, montelukast and a placebo, this was undertaken on 63 children aged from 2 to 6 years with asthma-like symptoms [64]. In spite of a lack of power, the results suggest that FP (100 μg twice daily) has a beneficial effect on symptoms and montelukast (4 mg once daily) on blood eosinophil level when compared with the placebo. Except for a difference in one lung function parameter after 3 months between FP and montelukast in favour of the FP group, this study revealed no differences between FP and montelukast [64]. More studies with a higher number of patients need to be done comparing ICS with montelukast in this age group. However, no randomised clinical trials have been carried out in a head-to-head comparison of ICS with montelukast in infants/preschoolers with recurrent wheezing and a positive or negative API. These types of studies are necessary in order to ascertain which controller (*i.e.* ICS or montelukast) should be used in infants/preschoolers in accordance with their API result.

Conclusions

In infants and preschoolers, establishing diagnosis of asthma and implementing a management strategy appropriate for individual patients is challenging; in this age group, the symptoms suggestive of asthma (*e.g.* wheeze and cough) may be a clinical expression of a number of diseases with different aetiologies. It is unlikely that these different diseases would respond to the same therapeutic agents, resulting in confusion among medical professionals concerning the following: 1) which patients should be given anti-asthma treatment, and 2) when to start the anti-asthma treatment. Whilst accepting these uncertainties, practicing paediatricians may use the API in a clinical situation to identify those young children with recurrent wheezing who are at risk of the subsequent development of persistent asthma, and who are likely to benefit from preventative anti-asthma medication (*e.g.* ICS or LTRAs). In addition, if parents better understand the prognosis of early childhood recurrent wheezing (*i.e.* positive API), it may help adherence with treatment. However, a number of questions, as yet, remain unanswered, these include the most appropriate treatment for individual patients, including type of medication (*e.g.* short-acting β-agonist *versus* ICS *versus* LTRA), schedule (regular *versus* as needed) and dose (high dose *versus* low dose), and how to move from the current "one size fits all" therapeutic strategy towards a true stratified medicine. Answering these questions is amongst the most important challenges in paediatric pulmonology for the next decade.

Statement of Interest

J.A. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis. C.E. Rodriguez-Martinez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Merck Sharp & Dome and AztraZeneca. He has received payment from GlaxoSmithKline, AztraZeneca, MSD and Grunenthal for the development of educational presentations. A. Custovic has received research fees from GlaxoSmithKline, ALK, ThermoFisherScientific, Novartis and Aursinett.

References

1. Yunginger JW, Reed CE, O'Connell EJ, *et al.* A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. *Am Rev Respir Dis* 1992; 146: 888–894.
2. Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003; 361: 51–59.
3. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133–138.
4. Lowe L, Murray CS, Martin L, *et al.* Reported *versus* confirmed wheeze and lung function in early life. *Arch Dis Child* 2004; 89: 540–543.
5. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000; 82: 327–332.
6. Kovesi T, Schuh S, Spier S, *et al.* Achieving control of asthma in preschoolers. *CMAJ* 2010; 182: E172–E183.
7. Lowe LA, Simpson A, Woodcock A, *et al.* Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005; 171: 231–237.
8. Schultz A, Brand PL. Episodic viral wheeze and multiple trigger wheeze in preschool children: a useful distinction for clinicians? *Paediatr Respir Rev* 2011; 12: 160–164.
9. Young S, Sherrill DL, Arnott J, *et al.* Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol* 2000; 29: 331–340.
10. Ball TM, Castro-Rodriguez JA, Griffith KA, *et al.* Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000; 343: 538–543.
11. Celedon JC, Wright RJ, Litonjua AA, *et al.* Day care attendance in early life, maternal history of asthma, and asthma at the age of 6 years. *Am J Respir Crit Care Med* 2003; 167: 1239–1243.
12. Caudri D, Wijga A, Scholtens S, *et al.* Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med* 2009; 180: 491–498.
13. Castro-Rodriguez JA, Holberg CJ, Wright AL, *et al.* A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162: 1403–1406.
14. Boehmer AL. Paediatric asthma: everything that seemed to be certain no longer is. *Paediatr Respir Rev* 2010; 11: 185–190.
15. Henderson J, Granell R, Heron J, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63: 974–980.
16. Savenije OE, Granell R, Caudri D, *et al.* Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011; 127: 1505–1512, e14.
17. Spycher BD, Silverman M, Brooke AM, *et al.* Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008; 31: 974–981.
18. Smith JA, Drake R, Simpson A, *et al.* Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008; 177: 1358–1363.
19. Simpson A, Tan VY, Winn J, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010; 181: 1200–1206.
20. Bhatt JM, Smyth AR. The management of pre-school wheeze. *Paediatr Respir Rev* 2011; 12: 70–77.
21. Brand PL, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096–1110.
22. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000; 2: CD001107.
23. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995; 72: 317–320.
24. Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007; 42: 407–420.
25. Bisgaard H, Zielen S, Garcia-Garcia ML, *et al.* Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315–322.
26. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; 65: 407–410.
27. Garcia-Marcos L, Martinez FD. Multitrigger *versus* episodic wheeze in toddlers: new phenotypes or severity markers? *J Allergy Clin Immunol* 2010; 126: 489–490.
28. Sonnappa S, Bastardo CM, Wade A, *et al.* Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010; 126: 519–526.
29. Schultz A, Devadason SG, Savenije OE, *et al.* The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010; 99: 56–60.
30. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. *Pediatr Pulmonol* 2011; 46: 1175–1181.
31. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004; 114: 1282–1287.
32. Kurukulaaratchy RJ, Matthews S, Holgate ST, *et al.* Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003; 22: 767–771.

33. Caudri D, Wijga A, CM AS, *et al.* Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009; 124: 903–910, e1–e7.
34. Brand PL. The Asthma Predictive Index: not a useful tool in clinical practice. *J Allergy Clin Immunol* 2011; 127: 293–294.
35. Leonardi NA, Spycher BD, Strippoli MP, *et al.* Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011; 127: 1466–1472, e6.
36. Castro-Rodriguez JA, Cifuentes L, Rodriguez-Martinez CE. The asthma predictive index remains a useful tool to predict asthma in young children with recurrent wheeze in clinical practice. *J Allergy Clin Immunol* 2011; 127: 1082–1083.
37. Castro-Rodriguez JA. The Asthma Predictive Index: a very useful tool for predicting asthma in young children. *J Allergy Clin Immunol* 2010; 126: 212–216.
38. Guilbert TW, Morgan WJ, Krawiec M, *et al.* The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials* 2004; 25: 286–310.
39. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354: 1985–1997.
40. Global Initiative for Asthma. Global strategy for the diagnosis and management of asthma in children 5 years and younger, 2009. www.ginasthma.org
41. Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma 2007. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm Date last updated: August 28, 2007. Date last accessed: March 23, 2012.
42. Becker AB. Asthma in the preschool child: still a rose by any other name? *J Allergy Clin Immunol* 2008; 122: 1136–1137.
43. Morgan WJ, Stern DA, Sherrill DL, *et al.* Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005; 172: 1253–1258.
44. Kuehni CE, Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. *Eur Respir J* 2002; 20: 880–889.
45. Bisgaard H, Allen D, Milanowski J, *et al.* Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004; 113: e87–e94.
46. Wasserman RL, Baker JW, Kim KT, *et al.* Efficacy and safety of inhaled fluticasone propionate chlorofluorocarbon in 2- to 4-year-old patients with asthma: results of a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2006; 96: 808–818.
47. Chavasse RJ, Bastian-Lee Y, Richter H, *et al.* Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone. *Arch Dis Child* 2001; 85: 143–148.
48. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123: e519–e525.
49. Zeiger RS, Mauger D, Bacharier LB, *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365: 1990–2001.
50. Martinez FD, Chinchilli VM, Morgan WJ, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2011; 377: 650–657.
51. Ducharme FM, Lemire C, Noya FJ, *et al.* Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009; 360: 339–353.
52. Svedmyr J, Nyberg E, Thunqvist P, *et al.* Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999; 88: 42–47.
53. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993; 68: 85–87.
54. Csonka P, Kaila M, Laippala P, *et al.* Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. *J Pediatr* 2003; 143: 725–730.
55. Daugbjerg P, Brenoe E, Forchhammer H, *et al.* A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr* 1993; 82: 547–551.
56. Panickar J, Lakhanpaul M, Lambert PC, *et al.* Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009; 360: 329–338.
57. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. *Lancet* 2003; 362: 1433–1438.
58. Grant CC, Duggan AK, DeAngelis C. Independent parental administration of prednisone in acute asthma: a double-blind, placebo-controlled, crossover study. *Pediatrics* 1995; 96: 224–229.
59. Vuillermin P, South M, Robertson C. Parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children. *Cochrane Database Syst Rev* 2006; 3: CD005311.
60. Robertson CF, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 175: 323–329.

61. Bacharier LB, Phillips BR, Zeiger RS, *et al.* Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127–1135.
62. Valovirta E, Boza ML, Robertson CF, *et al.* Intermittent or daily montelukast *versus* placebo for episodic asthma in children. *Ann Allergy Asthma Immunol* 2011; 106: 518–526.
63. Knorr B, Franchi LM, Bisgaard H, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001; 108: E48.
64. Kooi EM, Schokker S, Marike Boezen H, *et al.* Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. *Pulm Pharmacol Ther* 2008; 21: 798–804.

Chapter 3

Problematic severe asthma

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SUMMARY: Problematic severe asthma is the description of children referred to specialist care with asthma not responding to standard therapy. The initial step is to ensure that the diagnosis is right, and to evaluate co-morbidities. The next step is a detailed multidisciplinary assessment, including, if possible, a home visit. More than half have "difficult asthma", which improves if the basic management is correct; this may not be possible, but if the basics are not right, they are not candidates for potentially toxic new therapies. The remainder are termed "severe therapy resistant" asthmatics, and an individualised treatment plan is developed after a detailed and invasive protocol of investigations, including bronchoscopy and assessment of the response to intramuscular triamcinolone. Most treatments are unlicensed, with the exception of omalizumab (Xolair®; Genentech, San Francisco, CA, USA), and the evidence base is poor. International collaborations will be essential if the mechanisms of severe therapy resistant asthma are to be understood, and evidence-based treatment delivered.

KEYWORDS: Adherence, airway inflammation, asthma exacerbation, persistent airflow limitation, steroid resistance

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Most paediatric asthma is easy to manage with low doses of inhaled corticosteroids (ICS), if they are administered regularly through an appropriate delivery device. Children who do not respond to high-dose ICS and additional controller therapies have an impaired quality of life, consume a disproportionate amount of resources and may die prematurely [1]. Although the numbers are small compared with those with well-controlled asthma, the burden of disease is great. The exact prevalence is hard to determine but is probably ~5% of all children with asthma or ~0.5% of the paediatric population [2].

The aim of this chapter is to review the approach to school-age children referred to specialist paediatric care because they are thought to have asthma but the prescribed treatment is not working. Such children should be systematically evaluated by a multidisciplinary team. Preschool wheezing syndromes will be considered very briefly at the end of the chapter because there is less evidence here.

The literature is fraught with loosely defined terms, such as "difficult asthma", "severe asthma" and many others. When evaluating both clinical and scientific studies, as always it is important to ask the correct question, which is "to what extent have the subjects been evaluated by a specialist

and observed over time?'' It is all too easy to succumb to the temptation of assuming that all children who are not responding to standard treatment have severe, therapy-resistant asthma. This was illustrated by a study in which azithromycin and montelukast were compared as add-on therapies for children symptomatic despite ICS and long-acting β_2-agonists (LABAs) [3]. Of the 292 children referred for inclusion, only 55 could be randomised, because most of the rest either did not have asthma at all or were not taking their treatment. It would be idle to suppose that the same mistake is not being made elsewhere.

Defining problematic severe asthma

This is the umbrella term used to describe the child who has been referred to the specialist because of ''asthma not responding to standard treatment'' [4]. It can be criticised because such children may not have asthma at all, or may only have very mild disease once simple management steps are properly taken. Perhaps ''problematic obstructive respiratory symptoms'' might have been a better term.

In the developed world, problematic severe asthma comprises: wrong diagnosis (''not asthma at all''); asthma with important co-morbidities (''asthma plus…''); difficult asthma (which can be improved if basic management is optimised); and severe, therapy-resistant asthma (which remains severe even if all basic steps are correct).

In low- and middle-income countries, the World Health Organization (WHO) has defined a further category, namely ''untreated severe asthma'', in which access to basic medicines, locally appropriate protocols and educational material are not available. Some of these children may in fact have ''severe, therapy-resistant asthma'' [5]. This is an important category globally but will not be discussed further in this chapter.

Patterns of symptoms prompting referral

Most paediatric definitions are arbitrary and not evidence based, unless otherwise stated. The symptom patterns are not mutually exclusive and are one or more of the following [6].

1) Persistent (most days, for at least 3 months) chronic symptoms (the need for short-acting β_2-agonists at least 3 times per week because of symptoms) of airways obstruction despite high-dose ICS (beclomethasone dipropionate (BDP) equivalent 800 mg·day^{-1}) and trials of conventional add-on medication (LABAs, leukotriene receptor antagonists (LTRAs) and oral theophylline in a low, anti-inflammatory dose). The requirement for high-dose ICS is conventional and arbitrary, and it should be noted that for most asthmatic children, the plateau of the dose–response curve may be 100 mg *b.i.d.* fluticasone (200 mg *b.i.d.* BDP equivalent) [7].

2) Type 1 brittle asthma [8–11]. The definitions and most data are arbitrary and from adult studies; we define this as dramatic within-day swings in peak flow over a prolonged period of time.

3) Recurrent severe asthma exacerbations despite attempts with medication to abort exacerbations, including trials of allergen avoidance, low-dose daily ICS [12, 13], intermittent or daily LTRAs [14] or intermittent high-dose ICS [15, 16]. Exacerbations have required either: at least one admission to an intensive care unit (ICU); or at least two hospital admissions requiring intravenous treatment; or two or more courses of oral steroids during the last year.

4) Type 2 brittle asthma [17]. Again, largely defined in adult studies, but in paediatrics, a rapid onset of an acute asthma attack requiring admission to a high-dependency unit at the very least [18].

5) Persistent airflow obstruction: post-oral steroid, post-bronchodilator Z score $<$-1.96 for forced expiratory volume in 1 second (FEV_1), with normative data from appropriate reference populations [19].

6) The necessity of prescription of alternate day or daily oral steroids to achieve control of asthma.

It seems likely that the pathophysiology and optimal management of these different patterns is not the same but this has yet to be proven. However, although there is some overlap, the distinction between exacerbations and baseline control is of fundamental importance and will be discussed in detail later.

What are the characteristics of the referral group?

Unlike in adults, there is no significant sex difference in the paediatric series [20]. Typically, children are highly atopic and, unlike in adults, there is no obvious neutrophil preponderance [18, 21–23]. The pattern of severity will vary depending on the healthcare system and the availability of specialists. In the UK practice: most children are atopic and on high-dose therapy; spirometry can vary from normal to severe obstruction with variable response to acute bronchodilator inhalation; exhaled nitric oxide fraction ($F_{E}NO$) may be normal or high and morbidity for many is considerable [20, 24]. Prescription of multiple courses of oral steroids, admissions to hospital and ventilation in intensive care are all common [20]. In countries where there is more ready access to high-level specialists, the pattern of disease may be milder [25].

Is it asthma at all?

The first step is clearly a detailed history and physical examination, with simple physiological testing. Clearly there is no absolutely diagnostic test for asthma but there are four key questions, which are often glossed over. Is the child and family describing true polyphonic expiratory wheeze or are the noises less specific [26]? Are there features on history and examination which suggest an alternative diagnosis? Is the child atopic? Does the child have evidence of variable airflow obstruction over time and with treatment?

In many parts of Europe there is no word to describe polyphonic wheeze and, even where there is, there is no guarantee that it will be used correctly [26]. Ideally, a paediatrician should determine whether the child has intermittent true wheeze. Of course, wheeze may be due to many other conditions, but its absence should at least raise doubts about an asthma diagnosis. A detailed history and examination is mandatory and a history of rectal prolapse or the presence of, for example, digital clubbing point to another diagnosis. Atopy should be determined both by skin-prick tests and specific serum immunoglobulin (Ig)E measurements, since the two may not be concordant [27, 28]. If a child referred as problematic severe asthma is non-atopic, then the diagnosis should be carefully reviewed. Finally, physiological testing is important (table 1). Any physiological test may be negative in asthma but the more the paediatrician seeks and fails to find variable airflow obstruction, the less likely the diagnosis of asthma. A negative bronchial challenge in an allegedly markedly symptomatic child excludes asthma as a cause of those symptoms.

Further diagnostic testing is driven by the clinical picture. Most would automatically perform a sweat test and chest radiograph, but testing should also be driven by local disease prevalence. If the diagnosis is not asthma, management is of the underlying condition.

Table 1. Physiological testing in problematic severe asthma

Clinic spirometry: any evidence of obstructive physiology
Increase in spirometry tests after acute administration of short-acting β_2-agonist
Peak flow variability during a short period of home monitoring
Challenge testing (provided there is no severe airflow obstruction): exercise, methacholine

It is asthma. What now?

The next two steps are an assessment of the apparent severity of asthma, and the identification of any co-morbidities. The role of co-morbidities has been

reviewed in detail elsewhere [6, 17, 29]. Identification of co-morbidities is part of every stage of the assessment. Some are easily identified at the first visit, *e.g.* obesity; others, in particular psychosocial issues, are identified at the nurse's home visit. Finally, gastro-oesophageal reflux is only formally tested at the final stage of investigation.

Severity is assessed in the following domains and also by considering future risk; again, all figures are arbitrarily defined. Level of current prescribed treatment: by definition, this will be at a high level if the child has been labelled "problematic severe asthma"; level of current baseline control of asthma over at least the preceding month; and immediate past (possibly over last 6 months) burden of asthma exacerbations, including number and severity.

The elephant in the room: domains of risk

Severe asthma is not merely a problem because of present symptoms but also because of future risks. These include: failure of normal lung growth (airway "failure to thrive") [30]; risk of future loss of asthma control; risk of future exacerbations; risk of phenotype change from episodic, viral to multi-trigger (mainly preschool children) [31]; risk of long-term chronic obstructive pulmonary disease (COPD) [32]; and risk of harm from medications.

Many of these risks are either unquantifiable, cannot be modulated, or both, but they should be used to inform the future research agenda. Failure of normal airway growth was most clearly described in the Childhood Asthma Management Program (CAMP) study, in which 25% of children, irrespective of treatment (nedocromil, budesonide or placebo) showed a decline with time in % predicted FEV_1 [30]. The mechanism is unclear but the implication is that these children may develop fixed airflow obstruction in adult life. The best long-term follow-up of severe childhood asthma is the Melbourne cohort [33], who are now around 50 years old [20]. 44% of the severe asthmatics in the cohort have developed COPD, and these were the children who had the worst impairment of lung function on recruitment at age 10 years [32]. Clearly these children did not have access to modern therapies and cannot be compared with severe childhood asthmatics today, but these data do sound an ominous warning.

Risk of harm from medications is pivotal in considering "beyond the guidelines" therapy. Almost by definition, children with severe, therapy-resistant asthma will be exposed to potentially toxic therapies, and determining which are least harmful, given the circumstances, is an important part of therapeutic decision-making.

Is it "asthma plus…"? The role of co-morbidities

Asthma plus obesity

This is the most easily determined co-morbidity. The relationships between asthma, nonspecific respiratory symptoms and obesity are complex. Obesity clearly leads to breathlessness which is not related to asthma [34], and evidence of reversible airway obstruction should be carefully sought before escalation of therapy in the obese. In the CAMP study, no significant association was found between body mass index (BMI) and many markers of asthma control; however, there was a decrease in the FEV_1/forced vital capacity (FVC) ratio with increasing BMI [35]. At least in adults, obesity leads to a pauci-inflammatory form of asthma [36], and consideration should be given to noninvasive measurement of airway inflammation prior to escalating ICS. Finally, obesity is itself a pro-inflammatory state, and may cause steroid resistance [37]. Clearly obesity is undesirable on many grounds, but identifying the problem and achieving weight reduction are by no means the same thing!

Asthma plus upper airway disease

The relationship between the upper and lower airway is hotly debated but of only theoretical importance in this context. The paediatrician must be careful not to confuse nonspecific upper

airway noises with wheeze. The upper airway should be examined carefully in all asthmatics seeking clues to an alternative diagnosis, and to identify morbidity which merits treatment in its own right. Upper airway symptoms may cause significant impairment in quality of life; if by treating them, asthma improves, then this is a significant bonus which should not be anticipated [38, 39]. One study suggested that obstructive sleep apnoea, which is a pro-inflammatory state, may be associated with lower airway neutrophilic inflammation [40]. The relevance of this to asthma is not clear.

Asthma plus dysfunctional breathing patterns

Many asthmatics also exhibit symptoms of hyperventilation and vocal cord dysfunction (VCD), which are only detected if a good history is taken. Symptoms which disappear when the child is asleep are very unlikely to be due to asthma [41]. Other clues include difficulty breathing in, throat tightness, paraesthesia, cramps in the hand, and stridor or wheeze loudest over the larynx. In such cases, the aid of a skilled physiotherapist, speech therapist or clinical psychologist should be sought.

Asthma plus gastro-oesophageal reflux

The relationship between respiratory symptoms and reflux is complex (table 2) [42]. The evidence implicating reflux as causal in severe asthma in children is limited. If asymptomatic reflux is found, treatment is unlikely to ameliorate the symptoms of asthma. If symptomatic reflux is suspected, a therapeutic trial is reasonable, but if there is no response, a pH study is recommended before escalating therapy [43]. In our hands, treatment of reflux has rarely impacted on asthma severity in school-age children, implying it is merely a coincidental finding [44].

Asthma plus food allergy

Food sensitisation is common in severe asthma. It is often unclear whether this relates to true food allergy. It is also unclear whether both severe asthma and food sensitisation reflect the underlying atopic predisposition, or food allergy is causally related to asthma [45, 46]. Since anaphylactic reactions may be particularly severe in asthmatics, aggressive management of both conditions is advisable.

It is definitely asthma. What now?

The next step in the protocol is a detailed multidisciplinary assessment, led by an experienced respiratory nurse. If experienced nurses are not available, other personnel should be used, including the family physician. The role of high-resolution computed tomography (HRCT), measurement of bronchial hyperresponsiveness (BHR) and the evaluation of other biomarkers has been discussed elsewhere [17, 47]. In summary, HRCT and measurement of BHR are used if there is diagnostic doubt, and the role of biomarkers in clinical management, as opposed to as a research tool, is uncertain. The main message of these assessments is that professors sitting in clinic have little or no idea about what is happening at home. The nurse will typically spend a morning with the family at the hospital, visit the home by arrangement, make contact with the general practitioner and, where appropriate, contact the child's school. A number of areas are addressed, and then the results are discussed in a multidisciplinary meeting.

Table 2. Gastro-oesophageal reflux and respiratory symptoms

Gastro-oesophageal reflux leads to aspiration and symptoms
Gastro-oesophageal reflux worsens bronchial hyperresponsiveness *via* neural activity from the lower oesophagus
Respiratory symptoms cause or exacerbate reflux
The two co-exist independently
Asthma medication such as theophylline could provoke reflux

Asthma education

All children will have been shown how to use their inhalers and given asthma educational material. However, it is essential to keep repeating the message because retention is poor. In our series, nearly 40% were not using their inhalers correctly, despite multiple previous sessions, and nearly 15% were using an inappropriate device (usually a metered-dose inhaler without a spacer) [48]. Advice about avoidance of triggers is also discussed, including allergens and detection and management of episodes of poor control or acute asthma attacks (see sections: Passive and active exposure to tobacco smoke and Allergen exposure; and [48]).

The environment around the home

Factors such as traffic pollution [49] and external aeroallergen exposure [50], for example, may have important effects on asthma. Less obvious factors within the neighbourhood, such as violence and socioeconomic level, may also affect asthma [51, 52]. Identifying such factors, however, may not mean that they can be or will be remedied.

Adherence to treatment

Doctors sitting in clinics are no better than 50% accurate (the equivalent to tossing a coin) in predicting the extent of adherence. We routinely collect prescription uptake data from primary care, to calculate the total amount of medication to which the child has access. Access to medication is not the same as using it; but no access means that the medication is certainly not being taken. At the home visit, the nurse will assess whether: medication is available within the house; medication is being stockpiled in its original wrappings; medication is so inaccessible within the house that it is not being used; medication is out of date; or even whether empty canisters are being used. Even quite young children are frequently left to take their medication unsupervised [53], and the extent to which parents directly oversee the taking of medication is checked. In our previously published study, medication issues contributed in nearly half of the children [54].

Passive and active exposure to tobacco smoke

Tobacco exposure (active or passive) is documented by measurement of urinary or salivary cotinine. Exposure to passive smoking is common in asthmatic children; the frequency of active smoking is unknown. Evidence of indoor smoking is noted at the home visit. There is increasing evidence that tobacco smoke exposure may lead to steroid-resistant asthma [55, 56]. Every effort should be made to help parents quit, including referrals to smoking-cessation clinics.

Allergen exposure

This is a controversial area. There is no doubt that aeroallergen sensitisation is common, that high levels of allergens to which the child is sensitised in the home in combination with viral infection gives a high odds ratio for admission to hospital with an asthma attack [13], and that multiple allergic sensitisations are associated with recurrent acute exacerbations [57–59]. No study has shown that reducing allergen burden in the home will improve asthma control in children with really severe asthma. However, multi-faceted intervention studies in less severely affected children, including components of allergen avoidance [60, 61], have demonstrated sustained benefit. In these groups, benefit may be as great as with treatment with ICS [62]. Studies in other groups, notably with house dust mite avoidance, have failed to show benefits [63]. These studies are of dubious relevance for many reasons [64]. House dust mite avoidance is time consuming and expensive, and is unlikely to be pursued efficiently in children with relatively minor problems. Indeed, many studies actually failed to reduce house dust mite levels at all. Many studies were

short term and used inefficient means of allergen reduction. Adults and children were often combined in the same study. Often there was no adjustment for the effects of seasonal viral infections.

Allergen exposure in schools might also be important, but this possibility is an even more difficult area in which to intervene [65]. There is at least biological plausibility for allergen reduction. Allergens cause steroid insensitivity by an interleukin (IL)-2- and IL-4-dependent mechanism [66, 67]. Many allergens also have non-IgE-mediated effects, for example proteolysis [68]. Thus, the logic of allergen avoidance in children with really severe asthma is strong. In our previously published study, furry pets were common culprits and there was great reluctance to address the problem [54].

Another aspect is assessing the accommodation for the presence of moulds. The existence of severe asthma with fungal sensitisation (SAFS) is controversial even in adults. Diagnostic criteria are shown in the table 3. There is considerable evidence that fungal sensitisation and exposure are associated with increased morbidity and severity of asthma, including really severe exacerbations [69–71]. It would seem simpler to undertake a trial of addressing mould exposure, possibly in combination with oral anti-fungals, before using toxic steroid sparing agents.

Psychosocial issues

In many cases, psychosocial issues are only identified at the home visit, where parents are more likely to talk openly about sensitive matters. It is not useful to try to determine if asthma caused psychosocial morbidity, or the other way around; rather, both should be treated on their merits. Neighbourhood factors can impact on asthma control, and there have been methodological studies showing that stress can increase eosinophilic inflammation and trigger asthma exacerbation [72–75]. Psychosocial issues can also manifest as dysfunctional breathing, including hyperventilation and VCD, which frequently co-exist with asthma. An important clue to these is the disappearance of symptoms while the child is asleep.

The multidisciplinary planning meeting

After completion of the collection of all these data, the next step is a detailed team discussion. In more than 50% of cases, it is clear that there are potentially reversible factors which account for the problem. It is, of course, easier to identify problems like adherence than to address them, but few if any would feel it was useful to perform bronchoscopy or give omalizumab (Xolair®; Genentech, San Francisco, CA, USA) if the child was not even taking ICS regularly. For those children in whom reversible factors have not been identified, and basic management is deemed to be good, a further programme of investigations is recommended.

Asthma appears to be severe and therapy resistant. What next?

As with much in the field, there is no evidence to support protocol here, which has been described in detail elsewhere [17]. The protocol is summarised in figure 1. In summary, the child is assessed

Table 3. Diagnostic criteria for severe asthma with fungal sensitisation

Clinical criteria for severe asthma (in section: Patterns of symptoms prompting referral)
Evidence of allergic sensitisation (positive skin-prick test or specific immunoglobulin E) to one or more of *Aspergillus fumigatus*, *Alternaria alternata*, *Cladosporium herbarum*, *Penicillium chrysogenum*, *Candida albicans*, *Trichophyton mentagrophytes* or *Botrytis cinerea*
No evidence of allergic bronchopulmonary aspergillosis (which is in any case rare in children with asthma)

on two occasions, before and after a steroid trial with a single intramuscular injection of triamcinolone, in the domains of: symptoms (asthma control test [76]); lung function (spirometry before and after acute administration of short-acting β_2-agonist); and airway inflammation (exhaled nitric oxide, induced sputum). A fibreoptic bronchoscopy is performed, with bronchoalveolar lavage (BAL) and endobronchial biopsy. The aim is to try to answer four key questions (table 4).

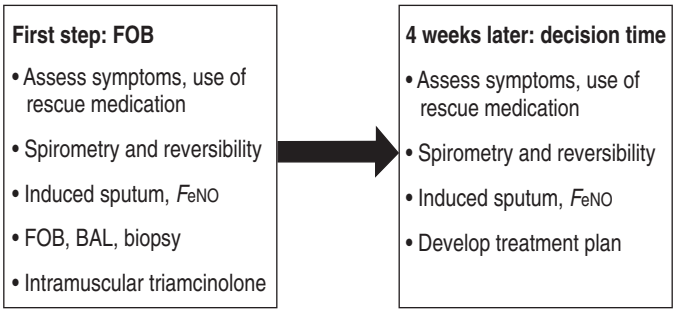
First step: FOB
• Assess symptoms, use of rescue medication
• Spirometry and reversibility
• Induced sputum, FeNO
• FOB, BAL, biopsy
• Intramuscular triamcinolone
4 weeks later: decision time
• Assess symptoms, use of rescue medication
• Spirometry and reversibility
• Induced sputum, FeNO
• Develop treatment plan

Figure 1. Protocol for the management of severe asthma. FOB: fibreoptic bronchoscopy; *F*eNO: exhaled nitric oxide fraction; BAL: bronchoalveolar lavage.

Some general issues will be discussed before each is considered in turn, and then treatment recommendations, which have been discussed in detail elsewhere [77], will be summarised.

General issues: what is meant by airway inflammation?

The tacit assumption is sometimes made that airway inflammation is homogeneous throughout the airway, proximal and distal, and in the lumen and the airway wall. This is not the case. At least in adults, transbronchial biopsy (TBB) has revealed disproportionate distal airway inflammation in people with poorly controlled asthma [78–80]. In children, there is only the poorest relationship between mucosal inflammation (measured on endobronchial biopsy) and luminal changes (induced sputum, BAL) [81]. The problem is that we cannot measure distal inflammation safely in children (TBB is not safe [82], and partitioning nitric oxide to proximal and distal gives too much overlap between normal and asthmatic patients to be clinically useful [83, 84]), and the evidence as to whether it is mucosal or luminal inflammation, which is important, is conflicting [81, 85].

Specific issues: why investigate severe, therapy-resistant asthma?

This section, which is not evidence based, summarises the information obtained from invasive investigations and how the information can be used to guide treatment. Treatment options are described in detail elsewhere in this issue of the *European Respiratory Monograph* (*ERM*) and in the published literature [77] and are summarised in table 5. In terms of steroid sparing agents, the only agent for that has a good evidence base in terms of randomised controlled trials is omalizumab [87–89]. However, many children with severe, therapy-resistant asthma have IgE levels so high that they are ineligible for treatment [20] and, in any event, every possible effort must be made to minimise allergen exposure before commencing this therapy. The others are either extrapolated from adult data or anecdotal. Omalizumab is discussed in more detail elsewhere in this issue of the *ERM*.

What is the pattern of airway inflammation?

Theoretically, inflammation could be classified as eosinophilic, neutrophilic or mixed, with the caveat that there may be differences between airway compartments (above). It is probable but not proven that targeting particular inflammatory patterns may be

Table 4. Questions to be answered by invasive investigation of severe, therapy-resistant asthma

What is the pattern of airway inflammation?
Is there concordance between symptoms and inflammation?
Does the child have steroid-responsive asthma?
Does the child have persistent airflow limitation?

Table 5. Summary of management options according to presenting problem, after a full assessment, including invasive tests

Problem	Treatment
Persistent chronic symptoms with eosinophilic inflammatory pattern	Ensure allergen burden as low as possible Very high-dose ICS SMART regime Consider use of theophylline to restore steroid sensitivity Trial of low-dose oral corticosteroids (preferably alternate day) Omalizumab (Xolair®; Genentech, San Francisco, CA, USA) if meets criteria [77] Steroid sparing agent (methotrexate, azathioprine, cyclosporine)
Persistent chronic symptoms with neutrophilic inflammatory pattern	Reconsider causes of neutrophilic inflammation (wrong diagnosis, reflux, tobacco smoke exposure) Wean steroids as far as possible (inhibit neutrophil apoptosis) Consider trial of macrolides Consider theophylline trial (accelerates neutrophil apoptosis)
Persistent chronic symptoms with mixed inflammatory pattern	Very poor evidence base. Consider combinations of eosinophilic and neutrophilic therapies
Persistent chronic symptoms with no airway inflammation	Wean anti-inflammatory therapy, monitoring closely Assess symptom perception Re-assess whether there is an issue with dysfunctional breathing patterns
Type 1 brittle asthma[#]	Ensure no residual airway inflammation when well Appropriate dose of ICS, plus either high-dose long-acting β_2-agonist (formoterol, which is preferred to salmeterol because of better dose–response characteristics [86]) or consider a double-blind trial of continuous subcutaneous terbutaline
Recurrent severe exacerbations	Ensure no residual airway inflammation when well (appropriate dose ICS) Ensure allergen exposure minimised Consider either or both of high-dose ICS or leukotriene receptor antagonist with exacerbations
Type 2 brittle asthma[¶]	Ensure no residual airway inflammation when well (ICS) Provide injectable adrenaline for emergencies
Persistent airflow obstruction	Reduce treatment to minimum If obliterative bronchiolitis is the cause, treatment can often be stopped altogether
Severe asthma with fungal sensitisation	Reduce exposure especially at home Check nebuliser for contamination Consider the use of itraconazole
Prescription of alternate day or daily oral steroids	Omalizumab (Xolair®; Genentech) if meets criteria [77] Steroid sparing agent (methotrexate, azathioprine, cyclosporine)

ICS: inhaled corticosteroids; SMART: Symbicort maintenance and reliever therapy (AstraZeneca, London, UK). [#]: chronic chaotic variation in peak flow; [¶]: sudden acute catastrophic deterioration on the background of apparently previously good asthma control.

useful. So, for example, there is some evidence that the use of macrolides may be helpful in neutrophilic asthma [90].

Is there concordance between symptoms and inflammation?

The concept of concordant and discordant phenotypes is based on adult studies [36]. In summary, discordant phenotypes are the polysymptomatic patient, with very little if any airway

inflammation, or the apparently asymptomatic patient with ongoing eosinophilic inflammation. This latter group may be an exacerbation-prone phenotype, which may benefit from intensification of therapy [91, 92]. The importance of the distinction from concordant phenotypes, in which inflammation and symptoms are closely related, is that it is the discordant group which may benefit from the use of inflammometry to monitor treatment. Certainly, it makes no sense to give ever more potent and potentially toxic anti-inflammatory therapies if the child has no evidence of airway inflammation.

Does the child have steroid-responsive asthma?

This is an area in which evidence is almost totally lacking. There is no agreed definition of steroid responsiveness in children and no consensus about the duration, dose or route of administration of the steroids for the purposes of the trial. Except in very rare cases of congenital steroid resistance [93], steroid responsiveness is a spectrum, and it is likely that in children at least, if enough steroids are given a response will be obtained in most. However, if the response is obtained only at the cost of intolerable side-effects, then it is hardly clinically useful. So, logically, any operational definition of steroid response must include an element of safety, and this shows individual variation, further complicating the matter. Since side-effects may take time to manifest, perhaps logically the concept of treatment resistance to safe doses of steroids is one that needs to be the subject of ongoing assessment.

The practicalities of a steroid trial have not been worked out in children. We know that 40 mg prednisolone daily for 2 weeks does not completely reveal the extent of steroid sensitivity, possibly as the result of adherence issues [94]. The use of depot triamcinolone will at least ensure that adherence is not an issue. Whether multiple doses would be better than a single dose has not been determined.

The adult definition of steroid responsiveness (failure to increase FEV1 by 15% after a 2-week course of prednisolone, while having an ongoing acute response to β_2 agonist of at least 15%) [95] is not useful in children, not least because many children with genuine severe, therapy-resistant asthma may have normal spirometry [10, 96]. There are several possible domains of responsiveness (table 6), which can be combined in various ways. Complete response to a single dose of triamcinolone or a 2-week course of prednisolone is unusual in our experience, which may reflect an inadequate dose or duration of the trial.

If the child is not steroid responsive by whatever definition is adopted, then the case for the use of non-steroid-based alternative treatments is compelling.

Does the child have persistent airflow limitation?

Persistent airflow limitation is defined by an FEV1 that remains <1.96 SD (Z) scores below normal, defined by appropriate data in a comparable normal population, despite maximal treatment.

Table 6. Possible criteria for steroid responsiveness in children with severe asthma

Domain	Requirement
Symptom response	Asthma control test [55] rises to $\geqslant$20 out of 25 or by $\geqslant$5
Lung function response	FEV1 rises to normal ($\geqslant$-1.96 Z score) or by $\geqslant$15% No residual bronchodilator response
Inflammatory response (if paired induced sputum samples available)	Sputum eosinophil count normal ($\leqslant$ 2.5%) [56]
Inflammatory response (if paired induced sputum samples not available)	F_{ENO}[#] normal (<24 ppb) [55]

FEV1: forced expiratory volume in 1 second; F_{ENO}: exhaled nitric oxide fraction. [#]: measured at a flow rate of 50 mL·s^{-1}. Symptom response: no improvement in any dimension; lung function response: one or two domains improve; inflammatory response: all three domains normalise.

The use of FEV1 is hallowed by time but it is of course a very insensitive measurement and it seems illogical to define persistent airflow limitation by such a crude marker. The diagnosis of obliterative bronchiolitis (OB) may be suspected from the finding of airway thickening and air trapping on a computed tomography (CT) scan, but it may be impossible to distinguish OB from asthma in an individual [97], so the diagnosis is made on physiological not imaging grounds. The nature of the steroid treatment trial is also contentious; a steroid trial is mandatory before the diagnosis is made, and we know that 2 weeks of prednisolone 40 mg daily is not sufficient (above). We do not know what an adequate steroid trial is, or how much bronchodilator should be trialled for how long at the end of the trial. The point of determining optimal lung function is clear, namely that there is no point in escalating treatment to try to reverse the irreversible. The practicalities are, however, much more difficult.

Special situations

The exacerbating phenotype

Asthma exacerbations cause disruption of daily life, may be life threatening, and may be associated with an accelerated decline in lung function [98]. There is little information in children with really severe asthma, and most has to be extrapolated from children with more mild disease. It has long been known that viral infection is a major trigger, but there has been increasing interest in the interactions between viruses and allergic sensitisation. These exacerbations are typically characterised by mixed eosinophilic and neutrophilic inflammation, or pure neutrophilic inflammation [99–102]. At the extreme, sudden exposure to a really heavy allergen load, as in thunderstorm asthma [103] and the Barcelona soya bean epidemic [104], is probably of itself sufficient to lead to an exacerbation with a distinctive eosinophilic phenotype [105], but this is the exception. We know that viral infections, with the exception of influenza, are not treatable, but this is no excuse for nihilism. Studies of the exacerbating phenotype have established important principles of management, demonstrated risk factors that are of interest mechanistically but cannot be addressed; and risk factors that can be modulated, as follows.

1) General principles. Although exacerbations and poor baseline control may co-exist, they are separate phenomena. Exacerbations are characterised physiologically by: an abrupt decline and then recovery in lung function and little day-to-day variability; poor baseline control is characterised by marked diurnal fluctuations [106, 107]. Exacerbations can occur on a background of good baseline control, and increasing interval medications to try to control exacerbations exposes the child to the risk of side-effects while not preventing exacerbations. No therapeutic strategy has ever been shown to completely abolish exacerbations.

2) Risk factors that are important mechanistically include genetic issues; CD14, CD16 [108] and the specific mucin glycan phenotype (O-secretor) have all been implicated [109].

3) There are other risk factors that can be modulated. A child who has had one severe attack is at risk of another [110, 111], although many children admitted to intensive care have hitherto had mild asthma [112]. There is a dose–response effect for allergic triggers, and children with multiple triggers are more vulnerable [57], suggesting that allergen avoidance is worthwhile. Children who have either or both of poor baseline control and poor lung function are also at risk [113].

From the latter two points, potential actions are suggested, which are summarised in table 7. Exacerbating adults with sputum eosinophilia have been successfully treated with the anti-IL-5 monoclonal antibody mepolizumab [92, 93], but this is not licensed in children, and indeed evidence that IL-5 is important is lacking in severe paediatric asthma.

Type 1 brittle asthma

Most of the data are from adults. Treatment options are summarised in table 2. This section summarises a protocol for trialling a continuous infusion subcutaneous terbutaline, if this is

Table 7. Management of the exacerbating child

Ensure they are taking low-dose ICS; but be aware there is no evidence that high-dose ICS give added benefit in this situation
Ensure that baseline control and lung function has been optimised
Determine the pattern of allergic sensitisation, and reduce allergen exposure as far as possible
Consider using measurements of airway inflammation to determine treatment in the following ways:
Non-invasively with induced sputum
Non-invasively with F_{ENO}
Bronchoscopically if very severe or frequent exacerbations

ICS: inhaled corticosteroids; F_{ENO}: exhaled nitric oxide fraction.

thought to be a viable option. The treatment is obviously demanding and has a strong placebo effect [114]. We therefore advocate a four-period, double-blind trial, usually as an in-patient. The child and family know that everyone except the pharmacist who prepares the solutions will be blinded to the treatment arm. We use a four-period design, because if the child is admitted, receives placebo and then active treatment, any improvement seen may be just from removal from a poor environment and accurate administration of medications in hospital, and indeed this is often what is seen. For a few children, this treatment is dramatically beneficial, and the inconvenience is worthwhile. The mechanism of benefit is not clear, perhaps very distal airways which are so obstructed that they cannot be reached by the inhaled route are targeted, but this is speculative. There are also concerns about possible desensitisation of β-receptors if the child has specific polymorphisms [115], but this is at the moment more of a theoretical risk.

Severe asthma with fungal sensitisation

Data in children are sparse [116]. There is one adult proof-of-concept trial suggesting that this entity responds to oral itraconazole [117], thus also giving justification for separating it off from the generality of severe, therapy-resistant asthma. If itraconazole is given, the risk of Cushing's syndrome with ICS must be remembered [118].

Vitamin D deficiency

Vitamin D is known to have many immunomodulatory properties [119] and there is increasing interest in the relationship between vitamin D levels and asthma control [120–122]. Most studies are in mild to moderate asthma, and there has been no intervention study giving vitamin D to children with severe asthma who are deficient in this vitamin. Nonetheless, it would seem sensible to measure vitamin D levels and supplement deficient children with severe asthma.

Monitoring therapy

There have been numerous papers proposing that monitoring asthma using exhaled nitric oxide, induced sputum and BHR improves outcomes [123–125]. The data supporting this approach in really severe asthma are few [126]. In one trial of 55 patients, half of whom were monitored using a strategy to normalise sputum eosinophils, there was no difference in outcome in the year-long time period [127]. A *post hoc* analysis suggested there was a reduction in exacerbations in the sputum eosinophil strategy group in the month after the measurements (they were seen every 3 months) [127]. Possible reasons for these disappointing results may include the following. 1) The group was insufficiently uniform and subgroups may have benefited. This underscores the need for collaboration, which is stressed later. 2) The fact that unlike in the adult study, sputum cellular phenotypes fluctuated over time [128]. 3) Induced sputum could not always be obtained, and the use of nitric oxide as a surrogate was not satisfactory as even within individuals there was no constant relationship between nitric oxide and airway eosinophilia [129].

At the present time there is insufficient evidence to recommend the routine use of inflammometry in the monitoring of these children, but here as elsewhere, more work is needed.

The preschool child with severe wheeze

There is even less evidence in this age group than in school-age children. Such evidence as there is in the first year of life would suggest that the prognosis is much better than for later wheeze, with many children becoming symptom free [130]. So, in the Oslo study, severe episodes of obstructive bronchitis in the first 2 years of age, but not the first year of life, were predictive of later asthma [131]. The younger the child, the more other diagnostic considerations become important. These are beyond the scope of this chapter, but in infants, acute bronchiolitis may be misdiagnosed as severe wheeze, given the imprecise way the term "wheeze" is used (above).

There is some evidence in older preschool children that detailed investigation with bronchoscopy and pH studies may yield useful information [132]. Clearly this approach is only justified if the problem is really severe. In these cases, uncontrolled eosinophilic inflammation or reflux may be found. Good quality outcome studies validating this approach are lacking, however. Much more work is needed in this field.

Overall summary and conclusions

It is obvious that children with problematic severe asthma should be assessed in a systematic manner. There is no point in giving beyond-the-guidelines asthma treatment to a child with an endobronchial foreign body, and no point in seeking severe asthma genes in a child who is not taking ICS regularly. Less than half of all children referred with "problematic severe asthma" in fact turn out to have true severe, therapy-resistant disease. Even children who have ongoing asthma symptoms after all basic management steps have been optimised, are a disparate group, with different patterns of inflammation. Therefore, it is unsurprising that so little is known about mechanisms, and that treatment is anecdote- not evidence-driven. If progress is to be made, then international collaborations such as those under the Global Allergy and Asthma European Network (GA_2LEN) initiative (see earlier), are essential. The key elements are: uniform and protocol-driven evaluation of each patient, so that centres can be confident that similar groups of patients are being studied; sharing of pathological material; uniformity of phenotyping; and the design of focussed studies to move the field forward. Ultimately, we should seek to determine why severe therapy resistant asthma develops; however, given our present lack of knowledge, this is indeed a target for the future.

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References

1. Fleming L, Wilson N, Bush A. Difficult to control asthma in children. *Curr Opin Allergy Clin Immunol* 2007; 7: 190–195.
2. Lang A, Carlsen KH, Haaland G, *et al.* Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. *Allergy* 2008; 63: 1054–1060.
3. Strunk RC, Bacharier LB, Phillips BR, *et al.* CARE Network. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol* 2008; 122: 1138–1144.
4. Bush A, Hedlin G, Carlsen KH, *et al.* Severe asthma in childhood: a common international approach. *Lancet* 2008; 372: 1019–1021.
5. Bousquet J, Mantzouranis E, Cruz AA, *et al.* Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; 126: 926–938.

6. Hedlin G, Bush A, Lodrup-Carlsen K, *et al.* Problematic severe asthma in children, not one problem but many: a GA^{2}LEN initiative. *Eur Respir J* 2010; 36: 196–201.
7. Lemanske R Jr, Mauger DT, Sorkness CA, *et al.* Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010; 362: 975–985.
8. Ayres JG, Miles JF, Barnes PJ. Brittle asthma. *Thorax* 1998; 53: 315–321.
9. Jenkins HA, Cherniack R, Szefler SJ, *et al.* A comparison of the clinical characteristics of children and adults with severe asthma. *Chest* 2003; 124: 1318–1324.
10. Bacharier LB, Strunk RC, Mauger D, *et al.* Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004; 170: 426–432.
11. Taylor DR, Bateman ED, Boulet LP, *et al.* A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008; 32: 545–554.
12. Covar RA, Szefler SJ, Zeiger RS, *et al.* Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008; 122: 741–747.
13. Murray CS, Poletti G, Kebadze T, *et al.* Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006; 61: 376–382.
14. Robertson CF, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 175: 323–329.
15. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000; 2: CD001107.
16. Ducharme FM, Lemire C, Noya FJ, *et al.* Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009; 360: 339–353.
17. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010; 376: 814–825.
18. Robinson DS, Campbell DA, Durham SR, *et al.* Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22: 478–483.
19. Stanojevic S, Wade A, Stocks J, *et al.* Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008; 177: 253–260.
20. Bossley CJ, Saglani S, Kavanagh C, *et al.* Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J* 2009; 34: 1052–1059.
21. Fitzpatrick AM, Gaston BM, Erzurum SC, *et al.* National Institutes of Health/National Heart, Lung and Blood Institute. Severe Asthma Research Program. *J Allergy Clin Immunol* 2006; 118: 1218–1225.
22. Moore WC, Bleecker ER, Curran-Everett D, *et al.* National Heart, Lung, Blood Institute's Severe Asthma Research Program. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Iimmunol* 2007; 119: 405–413.
23. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J* 2003; 22: 470–477.
24. Chipps BE, Szefler SJ, Simons ER, *et al.* Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2007; 119: 1156–1163.
25. Lang A, Mowinckel P, Sachs-Olsen C, *et al.* Asthma severity in childhood, untangling clinical phenotypes. *Pediatr Allergy Immunol* 2010; 21: 945–953.
26. Elphick HE, Ritson S, Rodgers H, *et al.* When a "wheeze" is not a wheeze: acoustic analysis of breath sounds in infants. *Eur Respir J* 2000; 16: 593–597.
27. O'Driscoll BR, Powell G, Chew F, *et al.* Comparison of skin prick tests with specific immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. *Clin Exp Allergy* 2009; 39: 1677–1683.
28. Frith J, Fleming L, Bossley C, *et al.* The complexities of defining atopy in severe childhood asthma. *Clin Exp Allergy* 2011; 7: 948–953.
29. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010; 36: 671–678.
30. Covar RA, Spahn JD, Murphy JR, *et al.* Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 2004; 170: 234–241.
31. Brand PL, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096–1110.
32. Tran H, Tai A, Roberts M. COPD: an outcome of childhood asthma? *Eur Respir J* 2010; 36: Suppl. 54, 1016s.
33. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol* 2002; 109: 189–194.
34. Carroll CL, Stoltz P, Raykov N, *et al.* Childhood overweight increases hospital admission rates for asthma. *Pediatrics* 2007; 120: 734–740.
35. Tantisira KG, Litonjua AA, Weiss ST, *et al.* Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax* 2003; 58: 1036–1041.
36. Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178: 218–224.
37. Sutherland ER, Goleva E, Strand M, *et al.* Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008; 178: 682–687.

38. de Benedictis FM, Bush A. Hypothesis paper: rhinosinusitis and asthma – epiphenomenon or causal association? *Chest* 1999; 115: 550–556.
39. Hellings PW, Hens G. Rhinosinusitis and the lower airways. *Immunol Allergy Clin North Am* 2009; 29: 733–740.
40. Li AM, Hung E, Tsang T, *et al.* Induced sputum inflammatory measures correlate with disease severity in children with obstructive sleep apnoea. *Thorax* 2007; 62: 75–79.
41. Niggemann B. Functional symptoms confused with allergic disorders in children and adolescents. *Pediatr Allergy Immunol* 2002; 13: 312–318.
42. de Benedictis FM, Carnielli VP, de Benedictis D. Aspiration lung disease. *Pediatr Clin North Amer* 2009; 56: 173–190.
43. Thakkar K, Boatright RO, Gilger MA, *et al.* Gastroesophageal reflux and asthma in children: a systematic review. *Pediatrics* 2010; 125: e925–e930.
44. Bechard DE, Schubert ML. Gastroesophageal reflux-induced asthma: new insights. *Gastroenterology* 1998; 114: 849–850.
45. Roberts G, Patel N, Levi-Schaffer F, *et al.* Food allergy as a risk factor for life-threatening asthma in childhood: a case controlled study. *J Allergy Clin Immunol* 2003; 112: 168–174.
46. Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. *Pediatr Pulmonol* 2007; 42: 489–495.
47. Lødrup Carlsen K, Hedlin G, Bush A, *et al.* Assessment of problematic severe asthma in children. *Eur Respir J* 2011; 37: 432–440.
48. Kamps AW, van Ewijk B, Roorda RJ, *et al.* Poor inhalation technique, even after inhalation instructions, in children with asthma. *Pediatr Pulmonol* 2000; 29: 39–42.
49. Spira-Cohen A, Chen LC, Kendall M, *et al.* Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. *Environ Health Perspect* 2011; 119: 559–565.
50. Codina R, Lockey RF, Fernández-Caldas E, *et al.* Identification of the soybean hull allergens responsible for the Barcelona asthma outbreaks. *Int Arch Allergy Immunol* 1999; 119: 69–71.
51. Sternthal MJ, Jun HJ, Earls F, *et al.* Community violence and urban childhood asthma: a multilevel analysis. *Eur Respir J* 2010; 36: 1400–1409.
52. Cohen RT, Canino GJ, Bird HR, *et al.* Violence, abuse., and asthma in Puerto Rican children. *Am J Respir Crit Care Med* 2008; 178: 453–459.
53. Orrell-Valente JK, Jarlsberg LG, Hill LG, *et al.* At what age do children start taking asthma medicines on their own? *Pediatrics* 2008; 122: e1186–e1192.
54. Bracken M, Fleming L, Hall P, *et al.* The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child* 2009; 94: 780–784.
55. Chaudhuri R, Livingston E, McMahon AD, *et al.* Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003; 168: 1308–1311.
56. Tomlinson JE, McMahon AD, Chaudhuri R, *et al.* Efficacy of low and high dose inhaled corticosteroid in smokers *versus* non-smokers with mild asthma. *Thorax* 2005; 60: 282–287.
57. Haselkorn T, Zeiger RS, Chipps BE, *et al.* Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2009; 124: 921–927.
58. Teach SJ, Crain EF, Quint DM, *et al.* Indoor environmental exposures among children with asthma seen in an urban emergency department. *Pediatrics* 2006; 117: S152–S158.
59. Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. *Cochrane Database Syst Rev* 2007; 1: CD001563.
60. Morgan WJ, Crain EF, Gruchalla RS, *et al.* Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004; 351: 1068–1080.
61. Kattan M, Stearns SC, Crain EF, *et al.* Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma. *J Allergy Clin Immunol* 2005; 116: 1058–1063.
62. Sheffer AL. Allergen avoidance to reduce asthma-related morbidity. *N Engl J Med* 2004; 351: 1134–1136.
63. Dust-mite control measures of no use. *Lancet* 2008; 371: 1390.
64. Platts-Mills TA. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol* 2008; 122: 694–696.
65. Almqvist C, Wickman M, Perfetti L, *et al.* Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001; 163: 694–698.
66. Kam JC, Szefler SJ, Surs W, *et al.* Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. *J Immunol* 1993; 151: 460–466.
67. Nimmagadda SR, Szefler SJ, Spahn JD, *et al.* Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics. *Am Rev Respir Crit Care Med* 1997; 155: 87–93.
68. Langley SJ, Goldthorpe S, Craven M, *et al.* Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitised, atopic asthmatic subjects. *Thorax* 2005; 60: 17–21.
69. O'Hallaren MT, Yunginger JW, Offord KP, *et al.* Exposure to aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991; 324: 359–363.

70. Neukirch C, Henry C, Leynaert B, *et al.* Is sensitization to Alernaria alternate a risk factor for severe asthma? A population based study. *J Allergy Clin Immunol* 1999; 103: 709–711.
71. Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk factor for life-threatening asthma. *Allergy* 2000; 55: 501–504.
72. Sandberg S, Paton JY, Ahola S, *et al.* The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356: 982–987.
73. Sandberg S, McCann DC, Ahola S, *et al.* Positive experiences and the relationship between stress and asthma in children. *Acta Paediatr* 2002; 91: 152–158.
74. Sandberg S, Javenpaa S, Penttinen A, *et al.* Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 2004; 59: 1046–1051.
75. Liu LY, Coe CL, Swenson CA, *et al.* School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med* 2002; 165: 1062–1067.
76. Schatz M, Sorkness CA, Li JT, *et al.* Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549–556.
77. Bush A, Pedersen S, Hedlin G, *et al.* Pharmacological treatment of severe, therapy resistant asthma in children: what can we learn from where? *Eur Respir J* 2011; 38: 947–958.
78. Kraft M, Djukanovic R, Wilson S, *et al.* Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996; 154: 1505–1510.
79. Sutherland ER, Martin RJ, Bowler RP, *et al.* Physiologic correlates of distal lung inflammation in asthma. *J Allergy Clin Immunol* 2004; 113: 1046–1050.
80. Kraft M, Martin RJ, Wilson S, *et al.* Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. *Am J Respir Crit Care Med* 1999; 159: 228–234.
81. Lex C, Ferreira F, Zacharasiewicz A, *et al.* Airway eosinophilia in children with severe asthma: predictive values of non-invasive tests. *Am J Respir Crit Care Med* 2006; 174: 1286–1291.
82. Whitehead B, Scott JP, Helms P, *et al.* Technique and use of transbronchial biopsy in children and adolescents. *Pediatr Pulmonol* 1992; 12: 240–246.
83. Paraskakis E, Brindicci C, Fleming L, *et al.* Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. *Am J Respir Crit Care Med* 2006; 174: 260–267.
84. Cohen J, Douma WR, ten Hacken NH, *et al.* Ciclesonide improves measures of small airway involvement in asthma. *Eur Respir J* 2008; 31: 1213–1220.
85. Regamey N, Tsartsali L, Hilliard TN, *et al.* Airway mucosa inflammation in children with cystic fibrosis. *Pediatr Pulmonol* 2007: Suppl. 30, 262–263.
86. Palmqvist M, Persson G, Lazer L, *et al.* Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997; 10: 2484–2489.
87. Humbert M, Beasley R, Ayres J, *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60: 309–316.
88. Massanari M, Milgrom H, Pollard S, *et al.* Adding omalizumab to the therapy of adolescents with persistent uncontrolled moderate-severe allergic asthma. *Clin Pediatr (Phila)* 2009; 48: 859–865.
89. Lanier B, Bridges T, Kulus M, *et al.* Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009; 124: 1210–1216.
90. Simpson JL, Powell H, Boyle MJ, *et al.* Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008; 177: 148–155.
91. Payne DN, Hubbard M, McKenzie SA. Corticosteroid unresponsiveness in asthma: primary or acquired? *Pediatr Pulmonol* 1998; 25: 59–61.
92. Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.
93. Nair P, Pizzichini MM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–993.
94. Lex C, Payne DN, Zacharasiewicz A, *et al.* Is a two-week trial of oral prednisolone predictive of target lung function in pediatric asthma? *Pediatr Pulmonol* 2005; 39: 521–527.
95. Goleva E, Hauk PJ, Hall CF, *et al.* Corticosteroid-resistant asthma is associated with classical antimicrobial activation of airway macrophages. *J Allergy Clin Immunol* 2008; 122: 550–559.
96. van Dalen C, Harding E, Parkin J, *et al.* Suitability of forced expiratory volume in 1 second/forced vital capacity versus percentage of predicted forced expiratory volume in 1 second for the classification of asthma severity in adolescents. *Arch Pediatr Adolesc Med* 2008; 162: 1169–1174.
97. Jensen SP, Lynch DA, Brown KK, *et al.* High-resolution CT features of severe asthma and bronchiolitis obliterans. Clin Radiol 2002; 57: 1078–1085.
98. O'Byrne PM, Pedersen S, Lamm CJ, *et al.* Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; 179: 19–24.
99. Warke TJ, Fitch PS, Brown V, *et al.* Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002; 57: 383–387.

100. Cai Y, Carty K, Henry RL, *et al.* Persistence of sputum eosinophilia in children with controlled asthma when compared with healthy children. *Eur Respir J* 1998; 11: 848–853.
101. Sur S, Crotty TB, Kephart GM, *et al.* Sudden-onset fatal asthma: A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis* 1993; 148: 713–719.
102. Carroll NE, Carello S, Cooke C, *et al.* Airway structure and inflammatory cells in fatal attacks of asthma. *Eur Respir J* 1996; 9: 709–715.
103. Marks GB, Colquhoun JR, Girgis ST, *et al.* Thunderstorm outflows preceding epidemics of asthma during spring and summer. *Thorax* 2001; 56: 468–471.
104. Ballester F, Soriano JB, Otero I, *et al.* Asthma visits to emergency rooms and soybean unloading in the harbors of Valencia and A Coru, Spain. *Am J Epidemiol* 1999; 149: 315–322.
105. Gibson PG, Norzila MZ, Fakes K, *et al.* Pattern of airway inflammation and its determinants in children with acute severe asthma. *Pediatr Pulmonol* 1999; 28: 261–270.
106. Reddel HK, Taylor DR, Bateman ED, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180: 59–99.
107. Reddel H, Ware S, Marks G, *et al.* Differences between asthma exacerbations and poor asthma control. *Lancet* 1999; 353: 364–369.
108. Martin AC, Laing IA, Khoo SK, *et al.* Acute asthma in children: relationships among CD14 and CC16 genotypes, plasma levels, and severity. *Am J Respir Crit Care Med* 2006; 173: 617–622.
109. Innes AL, McGrath KW, Dougherty RH, *et al.* The H antigen at epithelial surfaces is associated with susceptibility to asthma exacerbation. *Am J Respir Crit Care Med* 2011; 183; 189–194.
110. Miller MK, Lee JH, Miller DP, *et al.* Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007; 101: 481–489.
111. Belessis Y, Dixon S, Thomsen A, *et al.* Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol* 2004; 37: 201–209.
112. Robertson CF, Rubinfeld AR, Bowes G. Deaths from asthma in Victoria: a 12-month survey. *Med J Aust* 1990; 152: 511–517.
113. Haselkorn T, Fish JE, Zeiger RS, *et al.* Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009; 124: 895–902.
114. Payne DN, Balfour-Lynn IM, Biggart EA, *et al.* Subcutaneous terbutaline in children with chronic severe asthma. *Pediatr Pulmonol* 2002; 33: 356–361.
115. Taylor DR, Kennedy MA. Beta-adrenergic receptor polymorphisms and drug responses in asthma. *Pharmacogenomics* 2002; 3: 173–184.
116. Vicencio AG, Muzumdar H, Tsirilakis K, *et al.* Severe asthma with fungal sensitization in a child: response to itraconazole therapy. *Pediatrics* 2010; 125: e1255–e1258.
117. Denning DW, O'Driscoll BR, Powell G, *et al.* Randomized controlled trial of oral antifungal sensitization. The fungal asthma sensitization trial (FAST) study. *Am J Respir Crit Care Med* 2009; 179: 11–18.
118. De Wachter E, Vanbesien J, De Schutter I, *et al.* Rapidly developing Cushing syndrome in a 4-year-old patient during combined treatment with itraconazole and inhaled budesonide. *Eur J Pediatr* 2003; 162: 488–489.
119. Zacharasiewicz A, Wilson N, Lex C, *et al.* Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005; 177: 1077–1082.
120. Pijnenburg MW, Hofhuis W, Hop WC, *et al.* Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005; 60: 215–218.
121. Pijnenburg MW, Bakker EM, Hop WC, *et al.* Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005; 172: 831–836.
122. Sandhu MS, Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol* 2010; 105: 191–199.
123. Brehm JM, Schuemann B, Fuhlbrigge AL, *et al.* Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol* 2010; 126: 52–58.
124. Jartti T, Ruuskanen O, Mansbach JM, *et al.* Low serum 25-hydroxyvitamin D levels are associated with increased risk of viral coinfections in wheezing children. *J Allergy Clin Immunol* 2010; 126: 1074–1076.
125. Chinellato I, Piazza M, Sandri M, *et al.* Vitamin D serum levels and markers of asthma control in Italian children. *J Pediatr* 2011; 158: 437–441.
126. Brouwer AF, Brand PL. Asthma education and monitoring: what has been shown to work. *Pediatr Respir Rev* 2008; 9: 193–200.
127. Fleming LJ. The use of non-invasive markers of inflammation to guide therapy in children with severe asthma. MD Thesis. University of London, London, UK, 2009.
128. Fleming L, Wilson N, Regamey N, *et al.* Are inflamatory phenotypes in children with severe asthma stable? *Eur Respir J* 2007; 30: Suppl. 51, 483S.
129. Fleming L, Tsartsali L, Wilson N, *et al.* Discordance between sputum eosinophils and exhaled nitric oxide in children with asthma. *Thorax* 2008; 63: A34.

130. Mallol J, García-Marcos L, Solé D, *et al.* International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax* 2010; 65: 1004–1009.
131. Devulapalli CS, Carlsen KC, Håland G, *et al.* Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008; 63: 8–13.
132. Saglani S, Nicholson AG, Scallan M, *et al.* Investigation of young children with severe recurrent wheeze: any clinical benefit? *Eur Respir J* 2006; 27: 29–35.

Chapter 4

Asthma at school age and in adolescence

Susanne Lau and Ulrich Wahn

SUMMARY: At school age a more stable phenotype of asthma has developed. Most of the subjects are atopic. Different risk factors have been identified for the different phenotypes. Children with persistent wheeze in infancy and at school age are more likely to be atopic and have an increased risk of wheeze at age 13 years. Early sensitisation, especially to house dust mite, is a risk factor for asthma at school age that is associated with impaired lung function. Remission rates in adolescence are approximately 30%. During early puberty, approximately 3% of individuals develop new asthma. Asthmatics appear to be more susceptible for respiratory viral infections, often accompanied by exacerbations and hospital admission. Although, anti-inflammatory therapy cannot influence the development of lung function, sufficient symptom control can achieve a better quality of life. Allergen avoidance may reduce bronchial inflammation as a secondary measure in sensitised individuals. As primary prevention, early exposure to microbial antigens in farming communities and sufficient vitamin D levels could be identified.

KEYWORDS: Adolescence, asthma, outcome, protective factors, risk factors, school age

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Asthma in childhood (<13 years) and adolescence (13–18 years) is one of the most frequent chronic diseases and the clinical course can be quite heterogeneous. Approximately 60–75% of affected schoolchildren (5–18 years; however, school age can often refer to 5–11 years) are found to be atopic and show a lower rate of remission when compared with children without any atopic features (fig. 1)[1, 2].

During past decades a lot of epidemiological data aiming to analyse the risk and protective factors for asthma in order to explain the rising trend in prevalence has emerged [2, 3–5]. As different phenotypes exist many researchers have, therefore, tried to propose subtyping; for example, in accordance to the onset of wheeze and persistence from infancy to school age into early onset or persistent, late-onset and transient early (viral-induced) wheeze [6–9]. Prediction of persistence or remission remains difficult, many approaches have been proven not to be helpful in daily clinical practice [9]. However, the Tucson Children's Respiratory Study (TCRS; Tucson, AZ, USA) showed that patterns of wheezing prevalence and levels of lung function are established by 6 years

of age and do not appear to change significantly by the age of 16 years in children who started having asthma-like symptoms during their preschool years [10].

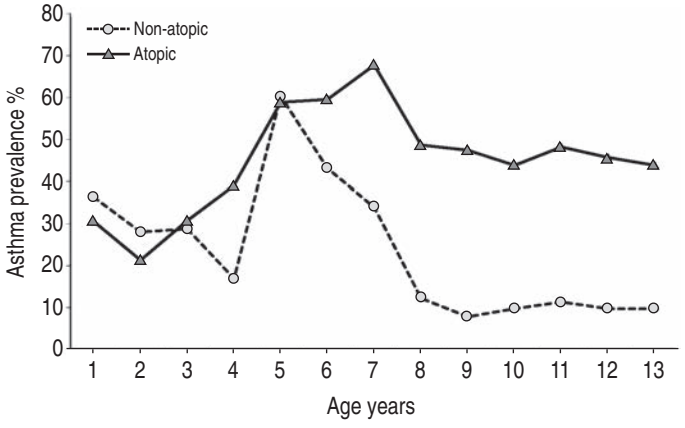

Figure 1. Asthma prevalence at school age (5–7 years) in atopic and non-atopic children. Reproduced from [1] with permission from the publisher.

In a cross-sectional trial, with more than 60 centres, the International Study of Asthma and Allergies in Childhood (ISAAC) showed that there is a large variation in the worldwide prevalence of asthma, suggesting that environmental and genetic factors play a role [11]. While there seems to be a rising trend with increasing "westernisation", low prevalence for asthma was found in Greece, China and Nigeria (less than 5%). The highest prevalence levels, *i.e.* over 25%, were found in the following English speaking countries: UK, USA, New Zealand, Australia and Costa Rica. In families who migrated from a low prevalence country to a high prevalence country it was observed that the children born in the new environment seemed to have adapted to the prevalence rates of the new country, indicating a major epigenetic and environmental influence [12]. Similar observations were made after German unification [13]. In Germany, the asthma prevalence was found to be 10% at school age (fig. 2) [2, 14] and the adaptation of the Turkish population to the German lifestyle and knowledge of the German language were associated with an increased risk for allergic rhinitis and asthma [15].

Asthma is a frequent chronic disease during school age and adolescence. Three quarters of affected individuals show atopy. Heterogeneity of the severity and course of the disease indicate that phenotyping is a prerequisite for understanding and controlling asthma. Different prevalence rates are found in different parts of the world suggesting a strong environmental or epigenetic influence.

Risk factors: early wheeze – later asthma?

Infections

Over 90% of children show immunoglobulin (Ig)G antibodies to respiratory syncytial virus (RSV) at the age of 24 months. However, only a certain percentage of these children experience lower respiratory tract infection (LRTI). It is not clear whether certain susceptibilities facilitate severe LRTI or whether a clinically apparent RSV illness causes bronchial hyperresponsiveness (BHR) and promotes the development of later asthma. LRTI caused by an RSV is associated with a three- to four-fold risk of subsequent wheezing during early school years [16–19]. Other viruses, predominantly rhinovirus, also play a major role in the development and exacerbation of asthma at school age [20–22]. There is increasing evidence to support the hypothesis that infections are associated with

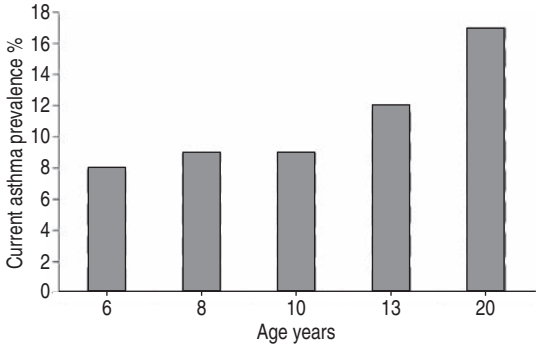

Figure 2. Asthma prevalence within the last 12 months at school age and adolescence in the German Multicenter Allergy Study. Data taken from [2] and unpublished data.

a greater morbidity in asthmatic subjects than in the healthy population, indicating a weaker antiviral response [23, 24].

Smoking

Maternal smoking during pregnancy is associated with a lower birth weight, decreased lung function and an increased risk for wheezing and specific sensitisation in high-risk children [25, 26]. Later in life environmental tobacco smoke exposure is a risk for severe asthma [27]. A study performed in the USA found that with increasing age asthmatic adolescents exhibited increasing rates of cigarette smoking [28]. Another study in Croatia showed that active and passive smoking had a harmful effect on the development of asthma during puberty in a high-school population and was associated with a higher total IgE level in serum [29].

Body mass index

There seems to be a U-shaped association between body mass index (BMI) and the risk for asthma [30]. On the one hand, low birth weight and being underweight later in life are risk factors for lower lung function and early wheeze [26, 31], on the other hand, obesity, especially in females with early menarche, is associated with asthma and asthma severity [32]. In a birth cohort study in the UK, it was shown that increasing BMI at 3, 5 and 8 years of age increased the risk of current wheezing at the corresponding age, and was more pronounced for girls than boys [33].

Sex

Until 13 to 14 years of age, the incidence and prevalence of asthma is greater among boys than girls [34–36]. During puberty and adolescence there seems to be a change in the sex ratio, with females showing greater incidences of asthma compared with males (fig. 3) [2, 35–37] , especially if they have their menarche before 11 years of age [32, 38, 39]. In addition, there is a greater proportion of males with remission when compared with females [36, 40]. The Childhood Asthma Management Program (CAMP) found that post-pubertal girls had greater airway responsiveness, even after adjustment for forced expiratory volume in 1 second (FEV_1) and other potential confounders, when compared with boys, indicating sex-specific factors [41]. Furthermore, young females were found to have more severe asthma [42, 43]. Early menarche seems to be associated

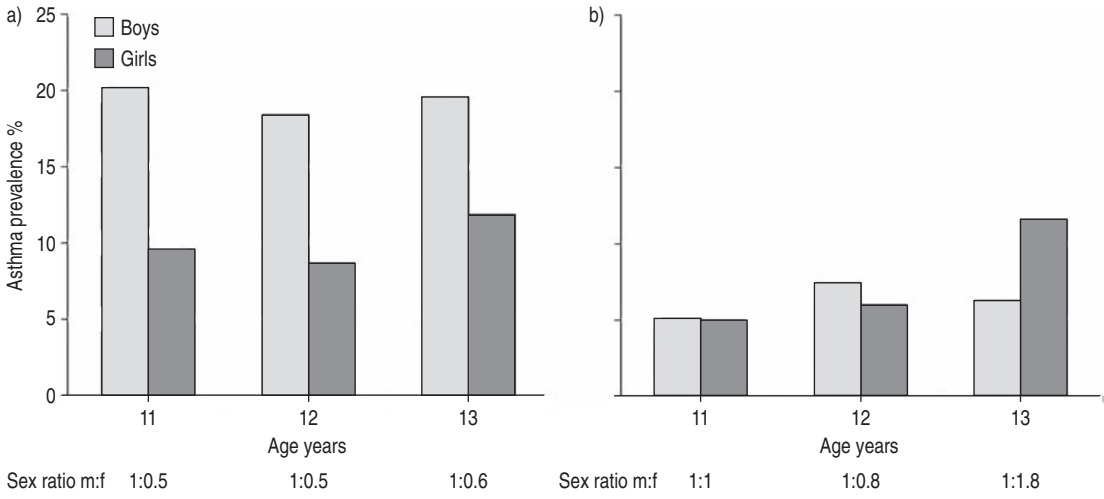

Figure 3. Asthma prevalence and change of sex ratio in adolescence in the German Multicenter Allergy Study. a) Resistance of wheeze in children with early wheeze. b) Late-onset of wheeze in children without early wheeze. M: male; F: female. Data taken from [2] and unpublished data.

with a stronger decline in lung function in asthmatic females [39], indicating that hormones may play a role in the process of bronchial inflammation and remodelling.

Socioeconomic disadvantage

Using nationally representative longitudinal data from the USA it appears that childhood socioeconomic status is strongly associated with the onset of chronic diseases like asthma (OR 1.47, 95% CI 1.4–1.55), hypertension, diabetes, heart attack and stroke in adulthood [44]. Low birth weight plays an important role in disease onset (OR for asthma 1.64, 95% CI 1.55–1.72) [44]. Although, it is known that atopy is often found in families with a higher levels of education. In the National Longitudinal Population-Based study in the USA, it was found that paternal education was negatively related to the risk of developing asthma, while maternal education was positively related (hazard risk for high school degree 1.49, 95% CI 0.98–2.26) compared to high school dropout [44].

Allergic sensitisation

Although asthma is more than an allergic inflammatory reaction to certain allergens and more than a skewed T-helper cell type 2 (Th2)-immune response, there is evidence that early immune responses in infancy and childhood may affect the development of asthma. Impairment of interferon-γ production at 3 months of age was associated with a greater risk of wheeze [45]. However, this is only true for the phenotype of asthma with associated atopy. Sensitisation to any allergen early in life and to inhalant allergens by the age of 7 years was found to increase the risk of being asthmatic at this age (OR 10), as described in the German Multicenter Allergy Study (MAS) and shown in figure 4 [46]. This was especially pronounced if a positive, parental history of asthma or atopy was present (OR 15), with the effect being strongest for maternal asthma. Children with sensitisation to house dust mites or pets at the age of 7 years and who were exposed to these indoor allergens were found to have declined lung functions [1].

In the Manchester Asthma and Allergy Study (MAAS), which was a population-based study, a machine learning approach was used to cluster children into multiple atopic classes in an unsupervised way. The relationship between these classes and asthma, up to the age of 8 years, was investigated. A five-class model indicated a complex latent structure, in which children with atopic vulnerability were clustered into four distinct classes (multiple early, multiple late, dust mite, and non-dust mite), with the fifth class describing children with no latent vulnerability. The association with asthma up to 8 years of age was considerably stronger for the multiple early class when compared with the other classes (OR 29 versus 12 versus 11 for multiple early class versus ever atopic versus atopic at 8 years of age, respectively) [47].

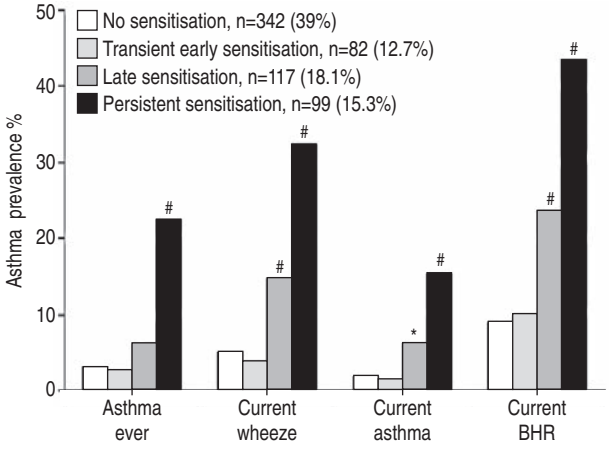

Figure 4. Prevalence of asthma symptoms at 7 years of age in the German Multicenter Allergy Study, stratified for sensitisation patterns. BHR: bronchial hyperresponsiveness. *: $p<0.05$; #: $p<0.0001$ compared to no sensitisation. Reproduced from [46] with permission from the publisher.

Exposure to animals

Although there is a clear association between the risk of asthma and sensitisation to pets, the exposure to pets has been reported to be potentially beneficial; however, the findings are inconsistent [48].

Allergic rhinitis as a predictor for wheezing onset in school-aged children

By the age of 13 years, the cumulative incidence of rhinitis was 47.8% in the German MAS [49]. Wheezing point prevalence was highest at the end of the second year, with a value of 19.8% decreasing to less than 7% during the following years [49]. The cumulative incidence of wheezing was 40.5% by the age of 13 years. Rhinitis at the age of 5 years significantly predicted the incidence of wheezing at the age of 5 and 13 years, with an adjusted relative risk of 3.82 ($p<0.001$). This association was not attributable to the type of sensitisation. In this group of children, 41.5% of all new cases of wheezing occurred among children with preceding allergic rhinitis. Wheezing was not a predictor for the incidence of rhinitis at either 5 or 13 years of age. Sensitisation was a predictor for wheezing and rhinitis.

Genetic factors

In epidemiological studies, parental history of asthma is the strongest risk factors compared with others, *e.g.* environmental exposure factors. However, it is well known that gene-by-environment interaction explains why exposure factors may have a different impact on individuals. Smoking may be especially harmful if certain polymorphisms are present [50]. Enzymes that detoxify inhaled agents (*e.g.* glutathione transferase genes) determine the effect of environmental pollution. DNA methylation or histone modification as epigenetic factors modify the transcription of genes (silencing, activation) and also explain different phenotypes in monozygotic twins [51]. A recent genome-wide association study identified the ORMDL3 gene on chromosome 17q21 as a risk factor for childhood asthma, possibly associated with increased interleukin (IL)-17 secretion in cord blood [52, 53]. Other studies reported more than 100 genes associated with asthma and allergy, however, findings cannot always be reproduced [54].

While eosinophils are more important in atopic asthmatics, neutrophils are predominantly found in bronchoalveolar lavage (BAL) samples of young children with wheezing. Both neutrophils and eosinophils may secrete matrix metalloproteinase (MMP)-9. MMP-9 plays an important role in airway wall thickening and airway inflammation. Certain gene variants for MMP-9 increase the risk of developing non-atopic asthma [55]. Polymorphisms in disintegrin and metalloprotease gene ADAM33 predict early life lung function at the age of 5 years [56].

Responses to pharmacotherapy, *e.g.* glucocorticoids, show a wide interindividual variability. Functional variants of the glucocorticoid-induced transcript 1 gene (GLCCI1) may partly explain the impaired response to inhaled glucocorticoids in patients with asthma [57].

Protective factors

Farm environment

Living on a farm, consumption of raw milk, and prenatal and post-natal contact with livestock were reported to protect against asthma and allergy [58]. In several studies of farming communities, the diversity of microbial exposure was inversely related to the risk of childhood asthma (OR 0.62 and 0.86) [59].

Early exposure to pathogens may have an impact on innate immunity and may cause an upregulation of certain toll-like receptors (TLRs). An alteration in TLR signalling can influence allergy and asthma development [60]. Functional relevant TLR1 and TLR6 variants were found to have a protective effect on atopic asthma [61].

Vitamin D and asthma

On the one hand, there has been increasing evidence for the protective effect of vitamin D [23, 62]. On the other hand, some studies have suggested a positive association between the level of vitamin D

intake and risk, for example, of atopic eczema [63]. Vitamin D deficiency may weaken pulmonary defences against respiratory infections and thus trigger asthma exacerbations in infancy and in school age [64]. In a study in CAMP study in the USA, lower vitamin levels were associated with increased airway responsiveness, higher IgE levels and greater likelihood of hospitalisation during asthma attacks in children [65, 66]. A possible mechanism of protection is the anti-inflammatory effect of vitamin D reducing the damage caused by viral induced inflammation.

Nutrition and asthma

Adherence to a Mediterranean type of diet, rich in polyunsaturated omega-3 fatty acid (olive oil) and oily fish, fresh fruits and vegetables, is associated with lower prevalence of asthma symptoms among 10–12-year-old children in the cross-sectional, PANACEA (Physical Activity, Nutrition, Alcohol, Cessation of smoking, Eating out of home And obesity) study [67]. The effect may be due to the antioxidants, which may reduce oxidative stress-related inflammatory disease.

Secondary prevention

Although allergen avoidance was not found to be protective as a primary measure [68], secondary prevention can be a successful approach in reducing the decline in lung function and chronic allergic inflammation in the bronchi for sensitised individuals. Children with sensitisation to indoor allergens and who had continuous exposure during the first 6 years of life were found to have poorer lung function than individuals with sensitisation but without significant exposure. Although some meta-analysis on house dust mite reduction and the effect on asthmatics showed inconsistent data [69], studies on monosensitised school-aged children could show a significant benefit for BHR [70].

Pharmacotherapy can reduce symptoms and may achieve asthma control; however, no influence on the natural course of the disease could be proven. In the CAMP study, treatment with inhaled corticosteroids (ICS) did not result in any higher post-bronchodilator lung function after 3 years of treatment, compared with nedocromil or placebo [71]. Maybe in the future new concepts of primary prevention will arise [72].

Prediction of outcome

Longitudinal studies revealed that approximately 30% of asthmatics with symptoms during childhood showed remission in adolescence and early adulthood [73]. However, of these 30% a certain percentage (approximately 12%, as in the Dunedin Multidisciplinary Health and Development Study undertaken in New Zealand) relapsed [37]. Risk factors for persistence and relapse are house dust mite sensitisation, smoking at 21 years, BHR and female sex. The earlier in age the onset of asthma occurs, the greater the risk of a relapse. However, asthma after relapse often seems to be mild [74]. A positive methacholine challenge at 15 years of age predicted a relapse of asthma at 26 years of age in the Dunedin study [74].

Persistent asthma from childhood to adolescence is associated with atopy, especially house dust mite sensitisation, increased BHR and poorer lung function compared to individuals showing remission of asthma at 18 years of age [74].

In the German MAS, approximately 3% of adolescents, aged between 10 and 13 years of age, developed new asthma [2]. Similar rates are reported between the ages of 18 and 21 years [74]. There seems to be different risk factors for asthma at the age of 11–13 years compared with children starting to wheeze before and after the age of 3 years. Perennial sensitisation is more important in children with early and later wheeze while atopic dermatitis was found to be a risk factor for children starting to wheeze after the age of 3 years. Parental atopy was predictive for both groups. A child with wheeze before the age of 3 years and sensitisation to indoor allergens (mite, cat or dog) had a probability as high as 75% of still having a wheeze at the age of 13 years.

The positive predictive value increased to 83% when a child with early wheezing and early sensitisation to indoor allergens was also exposed to high concentrations of indoor allergens early in life [4]. The study based in the Isle of Wight (UK) presented an algorithm comprising of four factors for childhood asthma: a family history of asthma; recurrent chest infections in infancy; absence of nasal symptoms at 1 year of age; and atopic sensitisation at age 4 years [5]. A third algorithm, based on the presence of atopic eczema, IgE sensitisation to food allergens and specific polymorphisms of the filaggrin gene, was able to predict another subset of asthmatic children in the German MAS cohort with a positive predictive value of 1.00 (95% CI 0.65–1.00) [2, 75].

Impact on quality of life

Quality of life (QoL) in chronic asthmatic disease seems to be mainly affected by control; the better the control of asthma the more enhanced the QoL. Severe uncontrolled asthma is associated with reduced lung function and impaired performance in physical exercise and impaired QoL [76]. In Dutch schoolchildren aged 7–10 years, the QoL scores among children and their caregivers were lower if the child had asthma with the lowest scores in diagnosed asthma compared with undiagnosed asthma and healthy controls [77].

Statement of Interest

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References

1. Illi S, von Mutius E, Lau S, *et al.* Perennial sensitisation early in life and chronic asthma in children. *Lancet* 2006; 368: 763–770.
2. Matricardi PM, Illi S, Grüber C, *et al.* Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008; 32: 585–592.
3. Arshad SH, Kurukulaaratchy RJ, Fenn M, *et al.* Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest* 2005; 127: 502–508.
4. Matricardi PM, Illi S, Keil T, *et al.* Predicting persistence of wheezing: one algorithm does not fit all. *Eur Respir J* 2010; 35: 701–703.
5. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009; 181: E181–E190.
6. Kurukulaaratchy RJ, Matthews S, Holgate ST, *et al.* Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003; 22: 767–771.
7. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing phenotypes in the first 6 years of life. *N Engl J Med* 1995; 332: 133–138.
8. Silverman M, Wilson N. Wheezing phenotypes in childhood. *Thorax* 1997; 52: 936–937.
9. Brand PL. The Asthma Predictive Index: not a useful tool in clinical practice. *J Allergy Clin Immunol* 2011; 127: 293–294.
10. Morgan WJ, Stern DA, Sherrill DL, *et al.* Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005; 172: 1253–1258.
11. Asher M, Björksten B, Lai CK, *et al.* Worldwide trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 733–743.
12. Wang HY, Wong GW, Chen YZ, *et al.* Prevalence of asthma among Chinese adolescents living in Canada and in China. *CMAJ* 2008; 179: 1133–1142.
13. von Mutius E, Martinez FD, Fritzsch C, *et al.* Prevalence of asthma., and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; 149: 358–364.
14. Lau S, Nickel R, Niggemann B, *et al.* The development of childhood asthma: lessons from the German Multicentre Allergy study (MAS). *Paediatr Respir Rev* 2002; 3: 265–272.
15. Grüber C, Illi S, Plieth A, *et al.* Cultural adaptation is associated with atopy and wheezing among children of Turkish origin living in Germany. *Clin Exp Allergy* 2002; 32: 526–531.
16. Sigurs N, Gustaffson PM, Bjarnason R, *et al.* Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am Respir Crit Care Med* 2005; 171: 137–141.
17. Sigurs N, Aljassim F, Kjellman B, *et al.* Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first years of life. *Thorax* 2010; 65: 1045–1052.

18. Stein RT, Sherill D, Morgan WJ, *et al.* Respiratory syncytial virus in early infancy: recurrent wheeze and allergy by age 13 years. *Lancet* 1999; 354; 541–545.
19. Stein RT. Long-term airway morbidity following viral LRTI in early infancy: recurrent wheezing or asthma? *Paediatr Respir Rev* 2009; 10: 29–31.
20. Jackson DJ, Gangnon RE, Evans MD, *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178: 667–672.
21. Midulla F, Pierangeli A, Cangiano G, *et al.* Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J* 2012; 39: 396–402.
22. Sears MD, Johnston NW. Understanding the September epidemic. *J Allergy Clin Immunol* 2007; 120: 526–529.
23. Bozzetti S, Carraro S, Giordano G, *et al.* Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy* 2012; 67: 10–17.
24. Jackson DJ, Johnson SL. The role of viruses on acute exacerbation of asthma. *J Allergy Clin Immunol* 2010; 125: 1178–1187.
25. Keil T, Lau S, Roll S, *et al.* Maternal smoking increases the risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy* 2009; 64: 445–451.
26. Midodzi WK, Row BH, Majaesic CM, *et al.* Early life factors associated with incidence of physician-diagnosed asthma in preschool children: results from the Canadian Early Childhood Development cohort study. *J Asthma* 2010; 47: 7–13.
27. James AL, Palmer LJ, Kicic E, *et al.* Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005; 171: 109–114.
28. Dowdell EB, Posner MA, Hutchinson MK. Cigarette smoking and alcohol use among adolescents and young adults with asthma. *Nurs Res and Pract* 2011; 2011: 503201.
29. Minaric A, Popovic GS, Nadalin S, *et al.* Passive smoking and respiratory allergies in adolescents. *Eur Rev Med Pharmacol Sci* 2011; 15: 973–977.
30. Tanaka K, Miyake Y, Arakawa M, *et al.* U-shaped association between body mass index and the prevalence of wheeze and asthma, but not eczema or rhinoconjunctivitis: the ryukyus child health study. *J Asthma* 2011; 48: 804–810.
31. Patelarou E, Chochlidaki M, Vivilaki V, *et al.* Is there a link between wheezing in early childhood and adverse birth outcomes? A systemic review. *Int J Environ Res Public Health* 2009; 6: 2752–2761.
32. Varraso R, Siroux V, Maccario J, *et al.* Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; 171; 334–339.
33. Murray CS, Canoy D, Buchan I, *et al.* Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Exp Allergy* 2010; 41: 78–85.
34. Bjornson CL, Mitchell I. Gender differences in asthma in childhood and adolescence. *J Gend Specif Med* 2000; 3: 57–61.
35. De Marco R, Locatelli F, Sunyer J, *et al.* Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000; 162: 68–74.
36. Nicolai T, Illi S, Tenborg, *et al.* Puberty and prognosis of asthma and bronchial hyper-reactivity. *Pediatr Allergy Immunol* 2001; 12: 142–148.
37. Godden DJ, Ross S, Abdallah M, *et al.* Outcome of wheeze in childhood. Symptoms and pulmonary function 25 years later. *Am J Respir Crit Care Med* 1994; 149: 106–112.
38. Al-Sahab B, Hamadeh MJ, Ardern CI, *et al.* Early menarche predicts incidence of asthma on early adulthood. *Am J Epidemiol* 2011; 173: 64–70.
39. Mascali F, Real FG, Plana E, *et al.* Early age of menarche, lung function, and adult asthma. *Am J Respir Crit Care Med* 2011; 183: 8–14.
40. De Marco R, Locatelli F, Cerveri I, *et al.* Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol* 2002; 110: 228–235.
41. Tantisira KG, Colvin R, Tonascia J, *et al.* Airway responsiveness in mild to moderate childhood asthma: sex influences on the natural history. *Am J Respir Crit Care Med* 2008; 178: 325–331.
42. Chen Y, Stewart P, Johansen H, *et al.* Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003; 56: 180–187.
43. Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnea in high-risk patients admitted for asthma: a 10-year retrospective study at Yale-New Haven Hospital. *Chest* 2001; 119: 115–119.
44. Johnson RC, Schoeni RF. Early-life origins of adult disease: national longitudinal population-based study of the United States. *Am J Public Health* 2011; 101: 2317–2324.
45. Celedon JC, Litonjua AA, Ryan L, *et al.* Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. *Arch Pediatr Adolesc Med* 2002; 156: 241–245.
46. Illi S, von Mutius E, Lau S, *et al.* The pattern of sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108: 709–714.
47. Simpson A, Tan VY, Winn J, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010; 181: 1200–1206.

48. Takkouche B, Gonzalez-Barcala FJ, Etminian M, *et al.* Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy* 2008; 63: 857–864.
49. Rochat M, Illi S, Ege MJ, *et al.* Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol* 2010; 126: 1170–1175.
50. Schultz EN, Devadason SG, Khoo SK, *et al.* The role of GSTP1 polymorphisms and tobacco smoke exposure in children with acute asthma. *J Asthma* 2010; 47: 1049–1056.
51. Fraga MF, Ballestar E, Paz MF, *et al.* Epigenetic differences during the lifetime of monozygotic twins. *Proc Nat Acad Sci USA* 2005; 102: 10604–10609.
52. Lluis A, Schedel M, Liu J, *et al.* Asthma-associated polymorphisms in 17q21 influence cord blood ORMDL3 and GSDMA gene expression and IL-17 secretion. *J Allergy Clin Immunol* 2011; 127: 1587–1594.
53. Moffatt MF, Kabesch M, Liang L, *et al.* Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007; 448: 470–473.
54. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006; 7: 95–100.
55. Pinto LA, Depner M, Klopp N, *et al.* MMP-9 gene variants increase the risk for non-atopic asthma in children. *Respir Res* 2010; 11: 23.
56. Simpson A, Maniatis N, Jury F, *et al.* Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-lung function. *Am J Respir Crit Care Med* 2005; 172: 55–60.
57. Tantisira KG, Lasky-Su J, Harada M, *et al.* Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. *N Engl J Med* 2011; 365: 1173–1183.
58. Loss G, Apprich S, Waser M, *et al.* The protective effect of farm milk consumption on childhood asthma and atopy: the GABRIELA study. *J Allergy Clin Immunol* 2011; 128: 766–773.
59. Ege MJ, Mayer M, Normand AC, *et al.* Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011; 364: 701–709.
60. Tesse R, Pandey RC, Kabesch M. Genetic variations in toll-like receptor pathway genes influence asthma and atopy. *Allergy* 2011; 66: 307–316.
61. Kormann MS, Depner M, Hartl D, *et al.* Toll-like receptor heterodimer variants protect from childhood asthma. *J Allergy Clin Immunol* 2008; 122: 86–92.
62. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Curr Opin Allergy Clin Immunol* 2009; 9: 202–207.
63. Back O, Blomqvist HK, Hernell O, *et al.* Does vitamin D intake during infancy promote the development of atopic allergy? *Acta Venereol* 2009; 89: 28–32.
64. Jartti T, Ruuskanen O, Mansbach MJ, *et al.* Low serum 25-hydroxyvitamin D levels are associated with increased risk of viral coinfections in wheezing children. *J Allergy Clin Immunol* 2010; 126: 1074–1076.
65. Brehm JM, Celedon JC, Soto-Quiros ME, *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009; 179: 765–771.
66. Brehm JM, Schuemann B, Fohlbrigge AL, *et al.* Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol* 2010; 126: 52–58.
67. Arvaniti F, Priftis KN, Papadimitriou A, *et al. Pediatr Allergy Immunol* 2011; 22: 283–289.
68. Woodcock A, Lowe LA, Murray CS, *et al.* Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; 170: 433–439.
69. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systemic review. *Allergy* 2008; 63: 646–659.
70. Ehnert B, Lau-Schadendorf S, Weber A, *et al.* Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992; 90: 135–138.
71. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma management Program Research Group. *N Engl J Med* 2000; 343: 1054–1063.
72. Martinez FD. New insights into the natural history of asthma: primary prevention on the horizon. *J Allergy Clin Immunol* 2011; 128: 939–945.
73. Sears MR, Greene JM, Willan AR, *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349: 1414–1422.
74. Taylor DR, Cowan JO, Greene JM, *et al.* Asthma in remission: can relapse in early adulthood be predicted at 18 years of age? *Chest* 2005; 127: 845–850.
75. Marenholz I, Kerscher T, Bauerfeind A, *et al.* An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol* 2009; 123: 911–916.
76. Lang A, Mowinckel P, Sachs-Olsen C, *et al.* Asthma severity in childhood, untangling clinical phenotypes. *Pediatr Allergy Immunol* 2010; 21: 945–953.
77. van Gent R, van Essen LE, Rovers MM, *et al.* Quality of life in children with undiagnosed and diagnosed asthma. *Eur J Pediatr* 2007; 166: 843–848.

Chapter 5

Physical exercise, training and sports in asthmatic children and adolescents

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SUMMARY: Exercise-induced asthma (EIA) is common in asthmatic children and adolescents. Treatment of childhood EIA is among the main aims of all international guidelines. Physical activity and fitness is found to improve with optimal control in children with EIA. Physical training does not improve asthma, but improves fitness and quality of life (QoL) in asthmatic children. Mechanisms of EIA include water loss and heat loss caused by increased ventilation during physical exercise, whereas the mechanisms of asthma development in adolescent athletes include respiratory epithelial damage, increased parasympathetic tone and airways inflammation leading to remodelling over time. In this chapter the basis for diagnosis of EIA and asthma in adolescent athletes and recommended treatment is discussed.

KEYWORDS: Asthmatic adolescent athletes, bronchial hyperresponsiveness, epithelial damage, exercise-induced asthma, exercise tests, inhaled steroids.

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Exercise-induced asthma (EIA) is common and sometimes the only manifestation of asthma in children and adolescents. EIA was defined by Aretaeus, the Cappodocian, 100 years AD [1]. In 1963, JONES *et al.* [2] published the first truly scientific paper on EIA, describing the fall in forced expiratory volume in 1 second (FEV_1) after exercise for 5–10 minutes, and the effect of different drugs given as pre-medication before exercise. 30 years ago it was stated that EIA occurred in 70–80% of asthmatic children not treated with inhaled steroids [3]. Exercise-induced bronchoconstriction (EIB) occurred in 8.6% of a normal population of 10-year-old children [4], was reported in 12% of non-asthmatic children aged 7–17 years [5] and among 36.7% of 10-year-olds with current asthma [4]. EIA and EIB are thus common manifestations of asthma in children. A joint task force of the European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) defined EIA as symptoms and signs of asthma occurring in an asthmatic after exercise, whereas EIB was defined as a reduction in FEV_1 of $\geqslant$10% after a standardised exercise test [6].

Pathogenic mechanisms of EIA

EIA is thought to be due to increased ventilation caused by the increase in demand for oxygen as a result of physical exercise. The increased ventilation is accompanied by heat and water loss as the inhaled air is warmed up to 37°C and is fully saturated with vapour through its passage down the airways. Consequently, the airways are cooled, giving rise to reflex parasympathetic nerve stimulation with resulting bronchoconstriction. Conservation of heat will be attempted by an initial vasoconstriction of the bronchial venules. When stopping exercise, the increased ventilation ceases, and so the need for conserving heat gives rise to a rebound vasodilatation. The result is both smooth muscle constriction and mucosal oedema in susceptible individuals [7], reducing the size of the bronchial lumen with increased airways resistance [8].

However, the increased water loss caused by the saturation of the inspired air due to the increased minute ventilation (V'_E) in exercise increases the osmolality in the extracellular fluid of the bronchial mucosa. The water loss from the bronchial mucosa induces movement of water from inside the cell to the extracellular space [9], thereby causing an intracellular increase in the ion concentration [10]. This may lead to the release of mediators, both newly formed eicosanoids and preformed mediators such as histamine, from intracellular granules and cause bronchoconstriction. It has been suggested that cold air mainly exerts its effect through the low water content of cold air, thus drying the respiratory mucosa [9].

The inflammatory basis of EIB was demonstrated by HALLSTRAND *et al.* [11]. They demonstrated a relationship between columnar epithelial cells in induced sputum and severity of EIB, and a relationship between cysteinyl leukotrienes and histamine *versus* columnar cells in sputum, demonstrating the role of mediator release. The same group also described the finding that MUC5AC, one of the gel forming mucins, was released after exercise challenge and related to the maximum fall in FEV_1 after exercise challenge, showing the role of mucin release in EIB [12].

Diagnosis of EIA in children

Respiratory symptoms, such as wheeze and cough, should, if occurring after physical exercise, raise the suspicion of asthma. Also EIA may be suspected in a child withdrawing from physical activity and play since children who experience respiratory problems with exercise may choose not to take part in exercise and play. This may even be unsuspected by parents [13]. It is important to verify suspected EIA by objective measurements in order to offer an optimal and sufficient treatment for EIA, because several other conditions may be confused with EIA. Whatever the cause, a child should receive help to master EIA as physical activity is an important part of a childs social interaction and development.

EIA may be verified by standardised exercise tests in the laboratory or exercise field tests and is looked upon as an indirect measure of bronchial responsiveness [14]. Other types of tests, such as the direct bronchial challenge by metacholine bronchial challenge, or indirect tests, such as the mannitol test, may suggest the presence of EIA [15], but not verify the diagnosis. Also a positive reversibility test, *i.e.* an increase in FEV_1 of at least 12% from before to after bronchodilator inhalation, may indicate asthma.

The diagnosis of EIA can be made by a standardised exercise test. The test should be standardised with regard to environmental temperature and humidity [16–18] and with a high exercise load, up to 95% of maximum exercise load, as measured by heart rate [19]. Free running tests have been found to be the type of activity best suited to provoke EIB, followed by running on a treadmill, whereas cycling and swimming are less provocative [17]. The exercise test has high specificity for asthma, but lower sensitivity, especially when the child is treated with inhaled steroids. Testing for direct bronchial responsiveness, through bronchial challenge with metacholine, has higher sensitivity, but lower specificity for the diagnosis of asthma [20–22].

Sports-specific field exercise tests are suggested to be much more sensitive in athletes compared with other tests [23], but this could not be verified by another study [22].

Clinically, EIA usually occurs shortly after heavy exercise. There is expiratory dyspnoea, coughing, audible rhonchi and sibilating rhonchi on lung auscultation with the symptoms of bronchial constriction usually reaching its maximum 6–10 minutes after the exercise.

Respiratory stridor occurring during maximum exercise in the well-trained adolescent child, often in girls, may be confused with EIA, but is due to vocal cord dysfunction (VCD). The stridor appears during inspiration with audible inspiratory sounds. EIA and VCD may coexist [24]. A maximal inspiratory flow at 50% of forced vital capacity (FVC) (MIF_{50})/maximal expiratory flow at 50% of FVC (MEF_{50}) ratio <1 after a metacholine bronchial provocation has been said to be typical of VCD [25]. Running on a treadmill at maximum intensity, with inspiratory stridor occurring during maximum intensity, can confirm the diagnosis, which may be further verified by continuous laryngoscopic exercise test [26, 27]. There are different treatment modalities for exercise-induced VCD that do not include asthma drugs, and endoscopic surgery has been found to be useful in selected patients [28].

Poor physical fitness and obesity should also be considered as possible differential diagnoses to EIA, and also other chronic respiratory or cardiac conditions.

Treatment and management of EIA

One of the main objectives of international asthma treatment guidelines for children is to enable children to fully participate in sports and physical activities [29, 30]. Treatment should focus on mastering EIA during childhood, including early childhood. Even in preschool-aged children with asthma, they mostly or partly avoid physical activity and tend to remain passive. The early identification of EIA, including objective measures to confirm the diagnosis, is an important part of the therapeutic procedure aimed at mastering EIA.

The primary aim of EIA treatment is to enable asthmatics to participate in physical activity and daily activities on an equal level with their healthy peers. The secondary therapeutic aim is to enable asthmatic children to fulfil their physical potential for participation in sports and to fulfil their ambitions.

Optimal control of EIA is most often obtained by anti-inflammatory treatment with inhaled corticosteroids (ICS) (table 1). The dose may vary according to asthma severity, and the effect occurs gradually, but with an early onset beginning after 1 week's treatment and improving further through the following weeks [33]. Additional control of EIA may be obtained by pretreatment before physical activity with bronchodilators such as inhaled short- or long-acting β_2-agonists [34], or ipratropium bromide [35]. Also leukotriene antagonists often improve control of EIA in children without the tolerance development often seen with regular treatment with inhaled β_2-agonists [32]. In severe asthma a fixed combination of inhaled steroids and long-acting β_2-agonists may increase control, especially in older children, but at the risk of possible tolerance development to the inhaled long-acting β_2-agonists.

A novel inhaled steroid, ciclesonide, may be of particular interest to athletes [36]. This steroid is a pro-drug, activated in the bronchial epithelium, which when passed into the blood stream is protein-bound and inactivated rapidly. The side-effects of this drug are thus limited both locally, *e.g.* oral candidiasis and hoarseness, as well as systemically, *e.g.* potential suppression of the adrenal glands. The potential adrenal suppression caused by most inhaled steroids may be particularly negative with respect to performance in sports [37]. Thus, particular attention to and avoidance of this side-effect is essential in top athletes where an optimal stress–response is required for optimal performance [38].

Table 1. Treatment for exercise-induced asthma (EIA)

Treatment type	Drug	Comment
Controller treatment	ICS	Presently the most important treatment available. Ciclesonide may be particularly suited for both children and athletes, due to lack of side-effects. For athletes, the lack of adrenal suppression may be of particular importance for performance [31].
	Leukotriene receptor antagonists	Montelukast protects against EIA without tolerance development. Several patients are non-responders [32]. Effect should be controlled through follow-up.
	Cromones	Effect uncertain.
Reliever treatment	Inhaled β_2-agonists	
	Short acting	Useful for pretreatment before exercise and for reliever treatment of dyspnoea. Regular use may cause tolerance development.
	Long acting	Useful with uncontrolled EIA both in schoolchildren and adolescent athletes. Regular use may give tolerance development. Should not be used without concomitant ICS.
	Anticholinergic drugs	May be particularly useful in athletes due to possible cholinerg involvement in pathogenesis.
	Inhaled ipratropium bromide	Can be used as premedication 45 minutes before exercise. Particularly useful in endurance athletes.
	Tiotropium	Not studied for EIA or in athletes. Potentially of importance in athletes.

ICS: inhaled corticosteroid.

Participation of asthmatic children and adolescents in physical activity and training

Physical training, in general, improves fitness, quality of life (QoL) and activity in asthmatic children [39, 40]. The participation in physical activity is important for a child's growth, long-term development and health [41]. Physical fitness has been related to psychological functioning in asthmatic children [42, 43].

The improved fitness and QoL obtained by participation in systematic physical training has been confirmed by a Cochrane based meta-analysis of eight training studies including 226 asthmatics from 6 years of age and above [44]. However, no change in lung function and bronchial responsiveness accompanied the increased physical fitness.

COUNIL *et al.* [45] confirmed improvement in aerobic and anaerobic fitness in asthmatic adolescents (mean age 13 years), but no improvement was found in lung function after 6 weeks training with high intensive bouts. FANELLI *et al.* [46] more recently reported improved QoL and also a reduction in severity of EIB, although not linearly related to improvement in fitness after 16 weeks of training in asthmatic children.

Some studies have demonstrated that asthmatic children are as physically fit and active as healthy children [47], whereas others have demonstrated that physical activity and fitness are related to asthma control and improves with optimal treatment with inhaled steroids and optimal asthma control [48]. Participation in planned physical training programmes may, thus, be an important part of rehabilitation for asthmatic children. A more active and happy life was obtained after participation in regular training groups planned for asthmatic children [40].

Regular physical activity should be part of daily life for children and adolescents with asthma.

Asthma and sports in children and adolescents

Why are asthma and bronchial hyperresponsiveness more frequent in athletes?

Increased prevalence of asthma and bronchial hyperresponsiveness (BHR) among young elite athletes were reported more than 20 years ago among swimmers [49] and cross-country skiers [50, 51]. Similar findings were later reported in Olympic athletes with regard to the use of asthma drugs [52]. The prevalence of asthma and BHR grew with increasing length of their active competitive period for both the Norwegian national team cross-country skiers [22] and for elite skiers [51]. In young adolescent swimmers a high prevalence of BHR was found at a young age, between 16 and 22 years, both assessed by metacholine bronchial provocation (provocative dose of metacholine causing a 20% fall in FEV_1 (PD_{20}) <4 μmol in 70.8%) and by eucapnic voluntary hyperpnoea (positive in 65%) [53].

The first report that showed intensive physical activity increased BHR was made more than 20 years ago, on adolescent elite swimmers aged from 12 to 18 years [49]. They swam three intervals of 1,000 meters and the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20} histamine) was measured before and after the swim. BHR increased both in asthmatic and healthy swimmers, but baseline PC_{20} histamine was significantly lower among swimmers with asthma. The increase in bronchial responsiveness correlated with the increase in exercise load (increase in blood lactate) during swimming in both asthmatic and healthy swimmers [49]. Later, SUE-CHU and co-workers [54, 55] showed that highschool, adolescent, cross-country skiers during one competitive winter season developed signs of inflammation (lymphoid follicles and deposition of tenascin, increased number of inflammatory cells) in their bronchial biopsies, independent of being asthmatics or not. Investigations in exercising animals demonstrate inflammatory changes in the airways. In addition, epithelial damage is a repeated finding. Mice, exercised by running, developed inflammation and epithelial damage in their airways compared with sedentary mice [56]. This was also found in Alaskan sledge dogs; examined by bronchoscopy and bronchoalveolar lavage before and after a sledge race across Alaska [57].

Increased neutrophil cell counts in induced sputum were found in swimmers and winter sport athletes, and the neutrophil counts correlated to the number of training hours per week in both groups [58]. Particularly in swimmers where eosinophil counts were increased, as was the number of bronchial epithelial cells [58]. Also in amateur endurance runners several inflammatory markers were found in induced sputum taken both before and after completing a half-marathon race; increased number of bronchial epithelial cells and apoptosis of bronchial cells, supernatant interleukin (IL)-8 levels of induced sputum and serum levels of Clara cell protein 16, were demonstrated as a measure of lung damage [59].

Extracellular water movement across cell membranes is important in the pathogenesis of EIA [9]. Aquaporin (Aqp) is a channel for aqueous water transport, driven by osmotic forces generated by sodium and chlorine ions and expressed in respiratory subepithelial glandular cells and alveolar type 1 cells of the lungs [60]. It has been reported that mice lacking the gene for the aqueous water channel Aqp5 have higher BHR to metacholine compared with normal mice [61]. PARK *et al.* [60] found a relationship between metacholine BHR and diminished pilocarpine-induced sweat secretion, tearing rate and salivary flow rate in athletes suspected of EIB indicating an autonomic dysfunction related to the measured BHR.

Intensive and regularly repeated training has been shown to influence autonomic regulation. Increased parasympathetic activity was reported by pupillometry in athletes, especially in endurance runners [62], whereas higher parasympathetic nervous activity was noted in top cross-country skiers and in children in training by using the ratio of resting ECG R-R-interval at full inspiration to the lowest R-R interval during 4 seconds of cycling as an index of vagal activity [35, 63].

The environment, in which physical training and sports are performed, is important for development of asthma and BHR both in children and athletes. During physical activity the exposure to inhalant environmental agents increases due to the increased V'_E during physical activity. With regular physical training and participation in sports activities this increases further.

The cumulative exposure to swimming pools has repeatedly been reported to increase asthma prevalence and EIA in Belgian children [64–67]. However, this was contradicted in a large English birth cohort study that reported cumulative swimming to be associated with increased lung function and a decreased risk of asthma symptoms, especially in children with pre-existing respiratory illness [68].

An epidemiological study, which included 3,535 South-Californian children, was performed in six areas with high pollution levels (ozone) and six with low pollution levels. After a 5-year follow-up period, children who participated actively in more than three types of sports in areas with high ozone levels were found to have an increased risk of asthma. Participating in sports in areas with low ozone levels did not increase the risk of asthma [69]. This is further supported by studies in athletes, especially endurance athletes. Young competitive swimmers develop BHR at an earlier age, earlier than competitive cross-country skiers [22, 53]. Increased inflammatory markers in induced sputum have been found in competitive swimmers [70, 71] and frequently BHR [53, 70, 71]. Increased leukotriene B_4 (LTB_4) levels in exhaled breath condensate were reported in Italian elite swimmers [72]. The environmental agent active in swimming pools is an organic chlorine product, thought to increase inflammation of the airways and BHR [73]

Cross-country skiers are repeatedly exposed to cold air [51], whereas athletes training and competing in ice rinks are at risk of exposure to oxides of nitrogen (NO_x) from the freezing machinery and to ultrafine particles from the resurfacing machines [74], corresponding to reports of high asthma prevalence among ice-hockey players [75] and figure skaters [76].

It is evident that the environmental conditions, in which physical training and sports are practised, have important implications for the respiratory health of active children and adolescents as well as for the adolescent athlete. Pollution and harmful chemicals in the environmental air increase the risk for asthma development and BHR in the child practising sports as well as for the competing athlete in endurance sports. Environmental precautions should be applied whenever possible. The effective mechanical ventilation system of swimming pools is important, and effort should be made to secure less harmful methods of disinfecting the water in swimming pools. Care should be taken not to practise outdoor sports and competitions in too cold an environment, with -15°C as a recommended lower limit. Alternatively cold protection equipment may be used, such as Lungplus (Lung-Plus Info AB, Hörby, Sweden) and Jonaset sports mask (Suomen Jonas OY, Helsinki, Finland). Endurance sports should not be carried out in areas with high air pollution. For the allergic athletes, exposure to aeroallergens may exacerbate asthma and allergic symptoms. The presence of concomitant allergic rhinitis may reduce QoL and sports performance [77].

Two main phenotypes of asthma may be described in athletes. The first group are those with asthma from early childhood, often accompanied by allergic sensitisation. Secondly, there are those athletes who contract their asthmatic symptoms through repeated heavy training and competitions for their sport [78, 79]. The primary lesion in this athlete's asthma is possibly epithelial barrier dysfunction caused by the frequently repeated periods of increased ventilation followed by airways inflammation and parasympathetic dominance [35, 58]. The latter may not have the obvious asthmatic symptoms caused by acute episodes of bronchoconstriction, but rather cough and phlegm over prolonged periods of time often provoked by repeated competitions and viral infections. The latter phenotype is not unlike chronic persistent asthma. Recently, it was suggested that athlete's asthma represented an ''endotype'' of asthma. An "endotype" is proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism [80]. It is unclear how this point of view would add to the understanding and treatment of asthma in athletes.

Diagnosis of EIA, asthma and BHR in competing adolescent athletes

For the athlete it is important that the suspicion of EIA should be confirmed by objective tests for two reasons; first, due to doping regulations, objective measures have been required to obtain approval for the use of asthma drugs in sports; secondly, intensive physical activity may produce increased amounts of respiratory secretions which may be confused with asthmatic symptoms. The objective tests, which may confirm an asthma diagnosis in the athlete, are as for asthmatic children, standardised exercise tests, exercise field tests, tests for BHR, such as metacholine bronchial challenge, or indirect tests, such as eucapnic voluntary hyperpnoea and mannitol test. Also the reversibility test; FEV_1 increase from before to after bronchodilator inhalation, can be indicative of asthma with a 12% increase in FEV_1 from before to after inhaled bronchodilator.

Eucapnic voluntary hyperpnoea [81], another indirect test of bronchial responsiveness, is a sensitive test of bronchial responsiveness in athletes, but physically demanding to perform [53]. Sports-specific field exercise tests have been maintained to be much more sensitive in athletes compared with other tests [23], but this could not be verified by another study [22]. Also inhalation of mannitol has been suggested as a substitute measure of EIA in athletes [15].

EIA usually occurs shortly after heavy exercise. The dyspnoea is expiratory with audible rhonchi and sibilating rhonchi on lung auscultation and the bronchial constriction usually reaches its maximum 6–10 minutes after stopping exercise. Often confused with EIA is the respiratory stridor occurring during maximum exercise load, inspiratory of character and representing exercise-induced VCD. First described by REFSUM *et al.* [82], and later in adolescents by LANDWEHR *et al.* [83], this condition often occurs among well-trained young girls, active in sports. EIA and VCD may coexist [24]. Exercise-induced VCD should be suspected with respiratory stridor occurring during maximum exercise intensity and is of inspiratory type, as described previously. There are different treatment modalities for exercise-induced VCD, although not including asthma drugs; even endoscopic surgery has been found useful in selected patients [28].

A chronic respiratory illness with reduced baseline lung function may give exercise limitations, and can be verified through demonstrating flow limitation in the tidal breathing flow–volume loop during exercise testing [84].

Therapeutic aspects of asthma in adolescent athletes

For athlete asthma anti-inflammatory treatment using inhaled steroids is most important, to reduce the inflammation caused by repeated training and competitions and possibly to help improve long-term prognosis. The treatment should follow regular treatment guidelines. Bronchodilators are frequently needed both as pretreatment before competitions and to relieve symptoms. Experience shows that inhaled ipratropium bromide is frequently an effective bronchodilator. Inhaled β_2-agonists, both short- and long-acting are often needed. It is important to assess objective measures like lung function and BHR when treating competitive athletes, as symptoms are frequently reported without clinical correlate.

For many years there have been strict regulations for the use of asthma drugs in sports. Initially, one feared that these drugs might improve performance, but now it is generally accepted that inhaled steroids and inhaled β_2-agonists do not improve performance, and the regulations have been loosened for most drugs, but not all (terbutaine). At present there are no restrictions for the use of inhaled steroids, inhaled ipratropium bromide, leukotriene antagonists and the inhaled β_2-agonists salbutamol, salmeterol and formoterol. However, inhaled terbutaline is restricted in competitive sports and objective measurements of BHR, EIB or bronchodilator reversibility must be documented for approval for its use. Physicians treating children and adolescents with asthma active in competitive sports should keep up-to-date on the doping rules and follow these in the selection of drugs and give the necessary documentation for the sports authorities.

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References
1. Adams F. The extant works of Aretaeus, the Cappodician. London, The Sydenham Society, 1856; pp. 316–319.
2. Jones RS, Wharton MJ, Buston MH. The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. *Arch Dis Child* 1963; 38: 539–545.
3. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise-induced asthma. *Thorax* 1985; 40: 481–487.
4. Lødrup Carlsen KC, Håland G, Devulapalli CS, *et al.* Asthma in every fifth child in Oslo, Norway: a 10-year follow-up of a birth cohort study. *Allergy* 2006; 61: 454–460.
5. Porsbjerg C, von Linstow ML, Ulrik CS, *et al.* Outcome in adulthood of asymptomatic airway hyperresponsiveness to histamine and exercise-induced bronchospasm in childhood. *Ann Allergy Asthma Immunol* 2005; 95: 137–142.
6. Carlsen KH, Anderson SD, Bjermer L, *et al.* Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008; 63: 387–403.
7. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, *et al.* Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979; 46: 467–475.
8. McFadden ER Jr, Nelson JA, Skowronski ME, *et al.* Thermally induced asthma and airway drying. *Am J Respir Crit Care Med* 1999; 160: 221–226.
9. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is… *J Allergy Clin Immunol* 2000; 106: 453–459.
10. Eveloff JL, Warnock DG. Activation of ion transport systems during cell volume regulation. *Am J Physiol* 1987; 252: F1–F10.
11. Hallstrand TS, Moody MW, Wurfel MM, *et al.* Inflammatory basis of exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2005; 172: 679–686.
12. Hallstrand TS, Debley JS, Farin FM, *et al.* Role of MUC5AC in the pathogenesis of exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 2007; 119: 1092–1098.
13. Brasholt M, Baty F, Bisgaard H. Physical activity in young children is reduced with increasing bronchial responsiveness. *J Allergy Clin Immunol* 2010; 125: 1007–1012.
14. Pauwels R, Joos G, Van der Straeten M. Bronchial hyperresponsiveness is not bronchial hyperresponsiveness is not bronchial asthma. *Clin Allergy* 1988; 18: 317–321.
15. Anderson SD, Charlton B, Weiler JM, *et al.* Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; 10: 4.
16. Stensrud T, Berntsen S, Carlsen KH. Humidity influences exercise capacity in subjects with exercise-induced bronchoconstriction (EIB). *Respir Med* 2006; 100: 1633–1641.
17. Anderson SD, Silverman M, Tai E, *et al.* Specificity of exercise in exercise-induced asthma. *Br Med J* 1971; 4: 814–815.
18. Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972; 47: 882–889.
19. Carlsen KH, Engh G, Mork M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000; 94: 750–755.
20. Anderton RC, Cuff MT, Frith PA, *et al.* Bronchial responsiveness to inhaled histamine and exercise. *J Allergy Clin Immunol* 1979; 63: 315–320.
21. Cockcroft DW, Davis BE, Todd DC, *et al.* Methacholine challenge: comparison of two methods. *Chest* 2005; 127: 839–844.
22. Stensrud T, Mykland KV, Gabrielsen K, *et al.* Bronchial hyperresponsiveness in skiers: field test *versus* methacholine provocation? *Med Sci Sports Exerc* 2007; 39: 1681–1686.
23. Rundell KW, Anderson SD, Spiering BA, *et al.* Field exercise *vs* laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. *Chest* 2004; 125: 909–915.
24. Elshami AA, Tino G. Coexistent asthma and functional upper airway obstruction. Case reports and review of the literature. *Chest* 1996; 110: 1358–1361.
25. Kenn K, Balkisson R. Vocal cord dysfunction: what do we know? *Eur Respir J* 2011; 37: 194–200.

26. Heimdal JH, Roksund OD, Halvorsen T, *et al.* Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *Laryngoscope* 2006; 116: 52–57.
27. Roksund OD, Maat RC, Heimdal JH, *et al.* Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. *Respir Med* 2009; 103: 1911–1918.
28. Maat RC, Roksund OD, Olofsson J, *et al.* Surgical treatment of exercise-induced laryngeal dysfunction. *Eur Arch Otorhinolaryngol* 2007; 264: 401–407.
29. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2011. www.ginasthma.org/
30. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. *Thorax* 2008; 63: Suppl. 4, iv1–121.
31. Agertoft L, Pedersen S. Lower-leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate. *Pediatr Allergy Immunol* 2010; 21: e199–e205.
32. de Benedictis FM, del Giudice MM, Forenza N, *et al.* Lack of tolerance to the protective effect of montelukast in exercise-induced bronchoconstriction in children. *Eur Respir J* 2006; 28: 291–295.
33. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. *Am Rev Respir Dis* 1983; 128: 993–997.
34. Carlsen KH, Rõksund O, Olsholt K, *et al.* Overnight protection by inhaled salmeterol on exercise-induced asthma in children. *Eur Respir J* 1995; 8: 1852–1855.
35. Knopfli BH, Bar-Or O. Vagal activity and airway response to ipratropium bromide before and after exercise in ambient and cold conditions in healthy cross-country runners. *Clin J Sport Med* 1999; 9: 170–176.
36. Subbarao P, Duong M, Adelroth E, *et al.* Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006; 117: 1008–1013.
37. Schwindt CD, Zaldivar F, Eliakim A, *et al.* Inhaled fluticasone and the hormonal and inflammatory response to brief exercise. *Med Sci Sports Exerc* 2010; 42: 1802–1808.
38. Heller MK, Laks J, Kovesi TA, *et al.* Reversal of adrenal suppression with ciclesonide. *J Asthma* 2010; 47: 337–339.
39. Basaran S, Guler-Uysal F, Ergen N, *et al.* Effects of physical exercise on quality of life, exercise capacity and pulmonary function in children with asthma. *J Rehabil Med* 2006; 38: 130–135.
40. Flapper BC, Duiverman EJ, Gerritsen J, *et al.* Happiness to be gained in paediatric asthma care. *Eur Respir J* 2008; 32: 1555–1562.
41. Scheett TP, Nemet D, Stoppani J, *et al.* The effect of endurance-type exercise training on growth mediators and inflammatory cytokines in pre-pubertal and early pubertal males. *Pediatr Res* 2002; 52: 491–497.
42. Strunk RC, Mrazek DA, Fukuhara JT, *et al.* Cardiovascular fitness in children with asthma correlates with psychologic functioning of the child. *Pediatrics* 1989; 84: 460–464.
43. Bender BG, Annett RD, Ikle D, *et al.* Relationship between disease and psychological adaptation in children in the Childhood Asthma Management Program and their families. CAMP Research Group. *Arch Pediatr Adolesc Med* 2000; 154: 706–713.
44. Ram FS, Robinson SM, Black PN. Effects of physical training in asthma: a systematic review. *Br J Sports Med* 2000; 34: 162–167.
45. Counil FP, Varray A, Matecki S, *et al.* Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr* 2003; 142: 179–184.
46. Fanelli A, Cabral AL, Neder JA, *et al.* Exercise training on disease control and quality of life in asthmatic children. *Med Sci Sports Exerc* 2007; 39: 1474–1480.
47. Berntsen S, Carlsen KC, Anderssen SA, *et al.* Norwegian adolescents with asthma are physical active and fit. *Allergy* 2009; 64: 421–426.
48. Vahlkvist S, Inman MD, Pedersen S. Effect of asthma treatment on fitness, daily activity and body composition in children with asthma. *Allergy* 2010; 65: 1464–1471.
49. Carlsen KH, Oseid S, Odden H, *et al.* The response to heavy swimming exercise in children with and without bronchial asthma. *In:* Morehouse CA, ed. Children and Exercise XIII. Illinois, Human Kinetics Publishers Inc., 1989; pp. 351–360.
50. Larsson K, Ohlsen P, Larsson L, *et al.* High prevalence of asthma in cross country skiers. *BMJ* 1993; 307: 1326–1329.
51. Heir T, Oseid S. Self-reported asthma and exercise-induced asthma symptoms in high-level competetive cross-country skiers. *Scand J Med Sci Sports* 1994; 4: 128–133.
52. Fitch KD. β_2-agonists at the Olympic games. *Clin Rev Allergy Immunol* 2006; 31: 259–268.
53. Stadelmann K, Stensrud T, Carlsen KH. Respiratory symptoms and bronchial responsiveness in competitive swimmers. *Med Sci Sports Exerc* 2011; 43: 375–381.
54. Sue-Chu M, Karjalainen EM, Altraja A, *et al.* Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers. *Am J Respir Crit Care Med* 1998; 158: 597–601.
55. Karjalainen EM, Laitinen A, Sue-Chu M, *et al.* Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med* 2000; 161: 2086–2091.
56. Chimenti L, Morici G, Paterno A, *et al.* Endurance training damages small airway epithelium in mice. *Am J Respir Crit Care Med* 2007; 175: 442–449.

57. Davis MS, McKiernan B, McCullough S, *et al.* Racing Alaskan sled dogs as a model of "ski asthma". *Am J Respir Crit Care Med* 2002; 166: 878–882.
58. Bougault V, Turmel J, St-Laurent J, *et al.* Asthma, airway inflammation, and epithelial damage in swimmers and cold-air athletes. *Eur Respir J* 2009; 33: 740–746.
59. Chimenti L, Morici G, Paterno A, *et al.* Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol* 2010; 298: L857–L862.
60. Park C, Stafford C, Lockette W. Exercise-induced asthma may be associated with diminished sweat secretion rates in humans. *Chest* 2008; 134: 552–558.
61. Nejsum LN, Kwon TH, Jensen UB, *et al.* Functional requirement of aquaporin-5 in plasma membranes of sweat glands. *Proc Natl Acad Sci USA* 2002; 99: 511–516.
62. Filipe JA, Falcao-Reis F, Castro-Correia J, *et al.* Assessment of autonomic function in high level athletes by pupillometry. *Auton Neurosci* 2003; 104: 66–72.
63. Knopfli BH, Bar-Or O, Araujo CG. Effect of ipratropium bromide on EIB in children depends on vagal activity. *Med Sci Sports Exerc* 2005; 37: 354–359.
64. Bernard A, Carbonnelle S, de Burbure C, *et al.* Chlorinated pool attendance, atopy, and the risk of asthma during childhood. *Environ Health Perspect* 2006; 114: 1567–1573.
65. Bernard A, Carbonnelle S, Michel O, *et al.* Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. *Occup Environ Med* 2003; 60: 385–394.
66. Bernard A, Carbonnelle S, Dumont X, *et al.* Infant swimming practice, pulmonary epithelium integrity, and the risk of allergic and respiratory diseases later in childhood. *Pediatrics* 2007; 119: 1095–1103.
67. Voisin C, Sardella A, Marcucci F, *et al.* Infant swimming in chlorinated pools and the risks of bronchiolitis, asthma and allergy. *Eur Respir J* 2010; 36: 41–47.
68. Font-Ribera L, Villanueva CM, Nieuwenhuijsen MJ, *et al.* Swimming pool attendance, asthma, allergies, and lung function in the Avon Longitudinal Study of Parents and Children cohort. *Am J Respir Crit Care Med* 2011; 183: 582–588.
69. McConnell R, Berhane K, Gilliland F, *et al.* Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002; 359: 386–391.
70. Moreira A, Delgado L, Palmares C, *et al.* Competitive swimmers with allergic asthma show a mixed type of airway inflammation. *Eur Respir J* 2008; 31: 1139–1141.
71. Helenius IJ, Rytila P, Metso T, *et al.* Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy* 1998; 53: 346–352.
72. Piacentini GL, Rigotti E, Bodini A, *et al.* Airway inflammation in elite swimmers. *J Allergy Clin Immunol* 2007; 119: 1559–1560.
73. Weisel CP, Richardson SD, Nemery B, *et al.* Childhood asthma and environmental exposures at swimming pools: state of the science and research recommendations. *Environ Health Perspect* 2009; 117: 500–507.
74. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol* 2003; 15: 237–250.
75. Lumme A, Haahtela T, Öunap J, *et al.* Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players. *Eur Respir J* 2003; 22: 113–117.
76. Mannix ET, Farber MO, Palange P, *et al.* Exercise-induced asthma in figure skaters. *Chest* 1996; 109: 312–315.
77. Bonini S, Bonini M, Bousquet J, *et al.* Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. *Allergy* 2006; 61: 681–692.
78. Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes-practical implications. *Allergy* 2008; 63: 685–694.
79. Moreira A, Delgado L, Carlsen KH. Exercise-induced asthma: why is it so frequent in Olympic athletes? *Expert Rev Respir Med* 2011; 5: 1–3.
80. Lotvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
81. Rosenthal RR. Simplified eucapnic voluntary hyperventilation challenge. *J Allergy Clin Immunol* 1984; 73: 676–679.
82. Refsum HE, Fõnstelien E, Oseid S, *et al.* Exercise-associated ventilatory insufficiency in adolescent athletes. *In*: Oseid S and Edwards AM, eds. The Asthmatic Child in Play and Sports. London, Pitmann Books Limited, 1983; pp. 128–139.
83. Landwehr LP, Wood RP 2nd, Blager FB, *et al.* Vocal cord dysfunction mimicking exercise-induced bronchospasm in adolescents. *Pediatrics* 1996; 98: 971–974.
84. Johnson BD, Weisman IM, Zeballos RJ, *et al.* Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999; 116: 488–503.

Chapter 6

Food allergy, asthma and anaphylaxis

Sarah Taylor-Black and Julie Wang

SUMMARY: Asthma and food allergy coexist in many children, although it remains unclear whether or not food allergy and asthma are simply associated with each other due to underlying predisposition to allergy or whether they are actually causally related. Several studies have shown that food allergic individuals who develop asthma are at higher risk for severe asthma. In addition, asthma in individuals with food allergy places those patients at higher risk for severe allergic reactions to food, such as anaphylaxis, particularly if the asthma is poorly controlled. Food allergy should be considered in children with acute, life-threatening asthma exacerbations with no identifiable triggers and in highly atopic children with severe persistent asthma resistant to medical management. Management of food allergy and asthma according to well-defined national guidelines is essential to establish good control of these conditions, particularly when they are concomitant. In patients with concurrent food allergy and asthma, education about heightened risks is an important step in treatment, and intramuscular epinephrine is the drug of choice in treatment of anaphylaxis.

KEYWORDS: Anaphylaxis, asthma, food allergy, prevalence

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Food allergy and asthma are common medical conditions of childhood, but it is unclear if they simply coexist due to predisposition to atopy or whether food allergy actually predisposes to worsening or more severe asthma. It is clear, however, that children with comorbid food allergy and asthma have increased morbidity. Children with both food allergies and asthma are at increased risk for severe anaphylaxis, including fatal and near-fatal anaphylaxis, particularly if the asthma is uncontrolled [1]. In this chapter, we will discuss the findings of recent studies which explore the relationship between food allergy and asthma, as well as review food-induced anaphylaxis and its relationship to asthma.

How does food allergy contribute to asthma?

In the community, there appears to be a strong perception that food allergy and asthma are linked, perhaps because they are well-known atopic conditions. This is reflected in the increasing literature investigating the relationship between food/diet and asthma [2]. In a survey of patients attending an asthma and allergy clinic, 73% believed that foods triggered their asthma symptoms [3].

Young children are often affected by food allergies, and these can precede the development of asthma and are considered a risk factor for persistent, problematic asthma [4–6]. There have been several studies which examine whether food allergy predisposes to asthma. For example, studies have shown that sensitisation to egg, one of the most common food allergens in childhood, is a risk factor for sensitisation to aeroallergens and asthma later in life [7, 8]. Although the majority of children eventually develop tolerance to egg [9], a recent case–control study investigated whether the natural history of food allergy had any impact on the risk for developing asthma [10]. Sixty-nine children with confirmed food allergies to egg and/or fish were followed until school-age. All of the children had developed tolerance to egg and 17% of those with fish allergy developed tolerance at follow-up. The authors found not only that sensitisation to egg was a marker for increased risk for later asthma, but that presence of asthma symptoms and bronchial hyperresponsiveness (BHR) were not associated with persistence of the food sensitisation. Moreover, there was no association between the severity of allergic reaction to foods and risk of developing asthma. In addition, wheezing is often a precursor to the development of asthma and the association between food sensitisation and viral-induced wheeze has been explored in a Finnish study [11]. Immunoglobulin (Ig)E antibodies for cod, milk, egg, peanut, soy and wheat were obtained in 247 hospitalised wheezing children aged 3 months to 16 years. Food allergen sensitisation was found to be associated with human rhinovirus-induced wheezing, although it was not associated with wheezing caused by other viruses [11].

The association between food allergy and asthma is further supported by epidemiologic studies demonstrating a high rate of food allergies in asthmatic children. The National Cooperative Inner City Asthma Study (NCICAS), which enrolled children with asthma from inner cities in the USA and collected serum samples, showed the prevalence of food sensitisation was surprisingly high, with 45% of the children having IgE-mediated sensitisation to at least one of the six most common food allergens (milk, egg, wheat, soy, peanut or fish) [12]. 4% of the children had IgE levels that indicated a very high likelihood (95% positive predictive value) of clinical reactivity. Data from the National Health and Nutrition Examination Survey (NHANES) has also demonstrated an increased prevalence of food sensitisation (to milk, egg, peanut and shrimp) and food allergy risk categories in those with asthma compared to those without asthma [13]. Evidence for this increased prevalence is particularly strong in those reporting current asthma and having had emergency department visits for asthma in the previous year. Of those with asthma, 27.5% had a detectable IgE level to at least one food and 1.9% had levels in the range that highly suggested clinical food allergy. In contrast, 14.9% of those without asthma had sensitisation to at least one food, and only 0.9% had levels that indicated probable food allergy.

Evidence from several studies have shown that children with asthma and concurrent food allergies tend to have worse asthma morbidity than those with asthma alone. From the NCICAS cohort, children with food sensitisation had higher rates of asthma hospitalisation and higher requirements of corticosteroid medications compared to those without food sensitisation [9]. The NHANES data demonstrated similar results; patients with asthma and food allergy were more likely to have had a severe asthma exacerbation compared to asthmatics without evidence of food allergy (OR 6.9, 95% CI 2.4–19.7) [13]. While these studies defined food allergies based only on serologic testing, a few studies have found associations between clinical food allergy and increased asthma morbidity. Roberts *et al.* [14] reported that children with life-threatening asthma (as defined by exacerbation requiring ventilation) were more likely to have a history of food allergy than children who had non-life-threatening asthma exacerbations (OR 8.58, 95% CI 1.85–39.71). Another study specifically examined the role of peanut allergy with asthma and found similar results [15]. Having peanut allergy was associated with higher rates of hospitalisation and use of systemic corticosteroids compared to asthmatics without peanut allergy.

A dose effect for the number and severity of food allergies with the likelihood of having a diagnosis of asthma has also been demonstrated [16]. Those who had severe allergic reactions to foods had higher rates of asthma, and those with milk, egg, and peanut allergies were independently associated with increased rates of asthma. This is in contrast to the study by Priftis *et al.* [10]

which found no correlation between the severity of egg or fish allergy with the risk of developing asthma. Another study found that children with food allergy presented with asthma at an earlier age than those without a history of food allergy. However, there was no association between asymptomatic food sensitisation and asthma prevalence or severity [16].

The role of food allergy in the development of asthma has been investigated in several studies by focusing on objective measurements of lung dysfunction associated with asthma. From a prospective study of unselected children, having an allergy to cow's milk was reported to be a predictor of later BHR and airway inflammation [17]. Children with IgE-mediated milk allergy diagnosed in infancy by oral food challenge had an increased risk of elevated BHR (using histamine challenge and exhaled nitric oxide) at 8 years of age. Similar results were reported by KROGULSKA *et al.* [18]; BHR (using methacholine challenge) was increased in food allergic children compared to healthy children without food allergy. Of note, these children did not have asthma or allergic rhinitis. In 1996, JAMES *et al.* [19] reported that oral food challenge-induced asthma was associated with increased BHR. However, rarely, increased BHR was observed in a participant with a positive food challenge but without respiratory symptoms [19]. Interestingly, respiratory symptoms were observed in only 26% of food allergic children during the oral food challenge, even in children with asthma [18]. Among those without asthma, 47% of food allergic children had increased BHR compared to 17% of children without food allergy, demonstrating a limitation of using BHR as a surrogate marker for asthma [18], as other studies have shown [20]. However, it is also possible that airway inflammation as evidenced by BHR may be a precursor of later asthma as some studies hypothesise [21, 22]. In addition, KULKAMI *et al.* [23] found that children with asthma and food allergies had significantly higher exhaled nitric oxide (22.4 *versus* 10.3; $p=0.01$) and sputum eosinophils (15.5 *versus* 2.0; $p<0.001$) compared with asthmatic children without allergies. Additionally, in a UK study investigating the exhaled nitric oxide fraction ($F_{E}NO$) in 94 peanut allergic children, children who had outgrown their asthma and children with a history of untreated wheezing had elevated levels of $F_{E}NO$, and these levels were significantly higher than those in children with treated asthma or those with no history of wheeze. This finding is concerning for ongoing eosinophilic airways inflammation in food allergic children, and may suggest a need for inhaled corticosteroid use in children with peanut allergy reported to have outgrown their asthma or children with untreated wheeze [24].

How does asthma affect food allergy?

Although lower respiratory symptoms [25] and occupational asthma [26, 27] can be triggered by food allergic reactions, food allergy generally does not present with chronic or isolated respiratory symptoms [25]. In a study of 279 asthmatics with a history of food-induced wheezing, 60% had a positive double-blind, placebo-controlled oral food challenge and, of these, 40% had wheezing as one of several symptoms [28]. Notably, only five subjects had isolated wheezing. In another large study with over 300 patients with both food allergy and atopic dermatitis, 27% of the positive double-blind, placebo-controlled oral food challenges manifested with pulmonary symptoms as part of the allergic reaction, with only 17% of these having wheezing, and very few patients having isolated wheezing [29]. Finally, although respiratory symptoms may not always accompany food allergic reactions, a concurrent diagnosis of asthma appears to worsen the general prognosis for food allergy. For example, the presence of asthma is a predictor for persistent cow's milk allergy [29, 30]. In addition, in a study of 807 children with cow's milk allergy, SKRIPAK *et al.* [31] found that asthma was associated with a lower likelihood of developing tolerance to milk. Most importantly, asthma is a risk factor for fatal food-induced anaphylaxis [1] and will be discussed later.

Asthma and food allergy in children: epidemiology

There appears to be an increasing prevalence of both food allergies and asthma in the past few decades. Unfortunately, it is difficult to determine the prevalence of asthma accurately due to the

lack of a gold standard diagnostic tool and the variable phenotypes of asthma. Based on self-reports of asthma, the incidence more than doubled between 1980 and 1996 [32], and now, nearly one (9.4%) in 10 children have asthma based on data from the 2008 National Health Interview Survey [33]. Similarly, the prevalence of food allergy is difficult to measure. The gold standard for food allergy diagnosis is a double-blind, placebo-controlled food challenge, which is labour intensive, time consuming and impractical in large-scale epidemiological studies. The majority of the available data is derived from surveys and measurement of specific IgE. Although these tools have various diagnostic limitations, studies employing these methods have reported consistent estimates of food allergy prevalence. The study by BRANUM and LUKACS [34], which used several national health databases and healthcare surveys, concluded that the prevalence of food allergy is US children was approximately 3.9%, an 18% increase in prevalence between 1997 and 2007. In a recent study from a minority urban multi-ethnic birth cohort, both self-reported Black race and African ancestry were associated with food sensitisation and a high number (at least three) of food sensitisations [35]. A study using serologic assessment of food allergy determined that 4.2% of children in the USA have a clinical food allergy [13]. Additionally, this study found that Black race, male sex and childhood age were risk factors for food allergy. Notably, these same demographic features are also risk factors for asthma [36]. The most recent US prevalence study of food allergy in children used data from an electronic survey, and reported a food allergy prevalence of 8.0% [37]. This study also reported that peanut, milk and shellfish were the most common allergies, and found that multiple food allergies were reported for 2.4% of all children, corresponding to 30.4% of children with food allergy. The odds of food allergy were significantly higher among Asian and black children *versus* white children. In addition, the odds were significantly lower among children in households with an income of $<$US$50,000 *versus* $\geq$US$50,000 [37]. In the UK, recent data from a general practitioner database of almost 3 million patients showed that the age–sex standardised lifetime prevalence rate was 0.51 per 1,000 patients in 2005, and the prevalence rate had doubled from 2001 to 2005. Interestingly, a significant inverse relationship between prevalence and socioeconomic status was also found in this study [38]. With regard to specific foods, the rates of peanut allergy in the USA and UK have doubled in the past decade, and it now affects approximately 1–2% of children [37, 39, 40].

Food-induced anaphylaxis and asthma

Food-induced anaphylactic reactions are not uncommon and account for more than one-third of the anaphylactic reactions treated in emergency departments [41]. Peanut, tree nuts, fish or shellfish are the foods most often implicated in these reactions [41]. In a US survey where medical records of patients followed in the Rochester Epidemiology study from 1983 to 1987 were examined, a food-induced anaphylaxis occurrence rate of 10.8 per 100,000 person-years was found [42]. Another study of food-induced anaphylaxis found seven cases of fatal food anaphylaxis evaluated during a 16-month period [43]. In 1992, SAMPSON *et al.* [44] reported six fatal and seven near-fatal (requiring intubation and vasopressor support) food-induced anaphylactic reactions in children from three metropolitan areas which were reported during a 14-month period. Common risk factors identified for these fatal and near-fatal reactions included asthma, failure to identify the responsible food allergen in the meal and previous allergic reactions to the incriminated food [44].

Symptoms of food anaphylaxis may develop within seconds to a few hours after ingestion of the food allergen, with the vast majority of reactions developing within the first hour. It is important to note that bronchospasm is often severe and largely refractory to β-agonists and can lead to severe hypoxia [41]. In cases of anaphylaxis, prompt administration of epinephrine is usually, although not always, lifesaving. In the study by PUMPHREY [45] of 48 cases of fatal anaphylaxis, three patients died despite receiving epinephrine from a self-administration kit appropriately at the onset of their reaction. In the review by BOCK *et al.* [1] of 32 fatal food anaphylaxis cases, two patients received epinephrine immediately but failed to respond.

As stated previously, asthma is a risk factor for fatal food-induced anaphylaxis [1]. In a recent study of anaphylaxis prevalence in the UK, those with asthma had significantly higher rates of

anaphylaxis compared to those without asthma [46]. Of note, the most common triggers for anaphylaxis in that population were drug and food allergies. Similar results were seen in a study from a managed care organisation in northern California (USA), which found a five times higher risk of anaphylactic shock due to food allergies in asthmatics compared to those without asthma [47]. The risk of anaphylaxis was higher in those with severe asthma (HR 8.23, 95% CI 6.59–10.27) compared to those classified as having non-severe asthma (HR 5.05, 95% CI 4.39–5.80). In addition, sub-optimally controlled asthma has recently been reported to be a risk factor for adverse reactions during oral immunotherapy to peanut [48].

In addition to anaphylactic reactions to ingestion of food allergens, inhalation of aerosolised food allergens can lead to severe symptoms. The earliest discussion of this topic was reported by DeBesche [49] in 1937, who described wheezing in patients after breathing fish odours. Bernhisel-Broadbent *et al.* [50] also described a patient who developed a ''fish asthma'' reaction after being exposed to steamed fish. Respiratory allergy to wheat proteins (baker's asthma) is one of the most common types of occupational asthma, and can also be caused by other cereals, such as rye, barley, rice, corn and oat [51]. However, this syndrome has been rarely described in children. Investigation of quantities of airborne peanut allergen have been performed in the past, and have shown that airborne Ara h1 (a major peanut protein) was undetectable in simulated real-life situations when participants consumed peanut butter, shelled peanuts and unshelled peanuts [52]. However, in 2008, a study investigating allergic reactions aboard commercial airliners, found inhalation of airborne food particles was the most commonly reported mode of exposure and, in many cases, reactions were reported to have started after peanuts were served and multiple bags were opened near the allergic passenger [53].

In addition, cases of food-dependent exercise-induced anaphylaxis have been reported. The first reports of these types of reaction were described in the late 1970s and early 1980s. The first reported case was exercise-induced anaphylaxis to shellfish. Four other cases of exercise-induced anaphylaxis were subsequently reported. One individual developed anaphylaxis when exercising within 2 hours following the ingestion of any food, and three patients developed symptoms whenever celery was ingested around the time of exercise [54, 55]. More recently, a sudden and unexpected death of an individual was described which was triggered by ingestion of hazelnuts and almonds followed by vigorous dancing [56]. In addition, in 2001, there was a Japanese case report of an 8-year-old girl experiencing fatal food-dependent exercise-induced anaphylaxis when she swam after eating buckwheat noodles [57].

Where do food-induced reactions occur?

Among patients with peanut and tree nut allergies, most initial reactions occurred at home, whereas most subsequent reactions happened outside the home [58]. A study in the UK showed that nearly 20% of the reactions in children occurred at school [59]. Most peanut and tree nut reactions at US schools occurred in the classroom and were due to craft projects using nuts or celebrations such as birthdays. However, a number of reactions also occurred in the playground or on school trips [60]. Regarding reactions in food establishments, most occurred in Asian food restaurants, ice cream parlours and bakeries or doughnut shops. 20% of reactions resulted from food in a buffet or a food bar [61].

Asthma and food allergy: unanswered questions

Asthma and food allergies coexist for many individuals and suffering from both illnesses worsens the prognosis. However, the relationship between these diseases is still unclear. It may be that children with both food allergy and asthma are more atopic in general, and this increased atopy is associated with severe, persistent and/or earlier onset asthma and food sensitisation, and there is no direct causal relationship between food ingestion and asthma. In 1995, a prospective, randomised, controlled study of cow's milk, egg and peanut avoidance investigating the

development of atopic diseases in 165 children in a high-risk (history of parental atopy) cohort found no difference between avoidance and non-avoidance groups regarding rates of food allergy, atopic dermatitis, allergic rhinitis, asthma, lung function or serum IgE level at age 7 years. However, children with a food allergy by age 4 years were more likely to have allergic rhinitis and asthma by age 7 years [62].

Current epidemiological studies are limited, mainly as rates of food sensitisation are based on serology alone and the clinical reactivity to potential allergens is not assessed. It is unclear how many of those patients would have an allergic reaction if exposed to these foods [13, 12]. In those studies, sensitisation to more foods and higher levels of sensitisation correlated with the severity of asthma. However, it is also known that some foods share homologous proteins with some environmental allergens and positive IgE tests may, in fact, be due to cross-reactive proteins. For example, individuals with birch tree pollen allergies can test positive to peanut [63, 64] and those with dust mite and/or cockroach allergies can test positive to shrimp [65], even when they are able to tolerate ingestion of these foods. A recent study reported that children sensitised to peanut but not birch more often reported symptoms to peanut ingestion compared to children sensitised to both peanut and birch (76% *versus* 46%, p=0.002) [64]. Furthermore, environmental allergies can be significant triggers for asthma [66]. In a study where 20% of children with reported food allergy also had asthma, the association between food allergy and asthma was stronger when subjects were stratified for concurrent sensitisation to aeroallergens [67]. Finally, in pollen-food allergy syndrome, sensitisation to aeroallergens, such as birch, mugwort or grass, can lead to oral symptoms such as mouth and throat itching to foods such as fresh fruits, vegetables and spices [68]. However, in this syndrome, less than 10% of patients with allergies to fresh fruits and vegetables experience systemic symptoms, with 9% experiencing symptoms outside of the gastrointestinal tract and 1.7% experiencing anaphylactic shock [69]. In general, these patients were actually noted to have more severe symptoms when they did not have clinical symptoms or a history of allergic rhinitis, indicating that this group of patients possibly had symptoms to the food that were not related to aeroallergen cross-reactivity [70]. No specific studies have been performed looking at whether patients with pollen-food allergy syndrome have worse or higher rates of asthma than patients with aeroallergen sensitisation alone without pollen-food oral symptoms.

It should be noted that for a subset of patients, respiratory symptoms, including wheezing, are induced by foods up to 30% of the time [18, 27, 28] and, as previously described, several reports have indicated that severe asthma is a risk factor for fatal food anaphylaxis [1]. Therefore, food-induced respiratory symptoms should be managed differently from asthma exacerbations triggered by other common environmental triggers; in the case of a food allergic reaction, injectable epinephrine is the treatment of choice as opposed to inhaled β-agonists.

Management of coexisting asthma and food allergies

Although it remains unclear whether or not food allergies and asthma are simply associated with each other or are causally related, there is abundant evidence that patients with both diagnoses are at risk for poor outcomes. These patients should, therefore, be well-managed to prevent potential morbidity and mortality. Making an accurate diagnosis of asthma and food allergies is the first step. A detailed history of asthma symptoms, triggers and response to bronchodilators is essential [71, 72]. Conventional asthma management, well detailed in national and international guidelines [73, 74], can achieve and maintain good control in the large majority of people with asthma. The recently published national guidelines by the National Institute of Allergy and Infectious Diseases (NIAID) provide a comprehensive review of the diagnosis and management of food allergy [75]. TThe guidelines should be used as a guide to determine appropriate testing, including the use of oral food challenges [75]. As with any medical condition, alternative diagnoses should be investigated, and for patients with possible asthma and food allergies, exercise-associated food-induced anaphylaxis, gastro-oesophageal reflux and vocal cord dysfunction (VCD) are additional disorders which must be considered in the differential diagnosis [71, 72].

In addition, food allergy may be suspected in special cases of children suffering from asthma, warranting appropriate work-up. These special cases may include acute life-threatening asthma with no identifiable triggers or severe asthma symptoms outside the typical season for viral infections. In addition, one may consider food allergy in highly atopic children with severe persistent asthma resistant to medical treatment in whom the history linking food ingestion to asthma may not be reliable due to fragmented care (*e.g.* children in foster care or children living alternatively with divorced parents) [76].

Treatment of food-induced anaphylaxis is similar to treatment of anaphylaxis as a result of other causes. Initial treatment must be preceded by a rapid assessment to determine the extent and severity of the reaction, and should be directed at maintenance of an effective airway and circulatory system. Intramuscular epinephrine is the drug of choice in treatment of anaphylaxis (table 1 and fig. 1). Epinephrine auto-injectors for self-administration should be prescribed to any individual at risk for food-induced reactions, and their prescription for food-allergic patients who have asthma or who have experienced a previous reaction involving the airway or cardiovascular systems is especially crucial [41]. Of note, according to the new National Asthma Education and Prevention Program (NAEPP) guidelines, although epinephrine auto-injectors are not generally used to treat asthma without concern for food allergic reaction, it is now recommended in special situations for the treatment of severe, refractory asthma-exacerbations in school-based settings [78].

Education regarding food allergy and asthma management is essential once the diagnosis of both food allergy and asthma are confirmed. Patients and their families should be aware of the importance of food allergen avoidance, as well as the appropriate use of emergency medications in cases of allergic reaction [75]. In particular because uncontrolled asthma is a risk factor for severe anaphylaxis; optimal management and compliance with controller asthma medication is required. It is important to note that patients can often be confused about whether symptoms are due to

Table 1. Summary of the pharmacological management of food-induced reaction, including anaphylaxis

First-line treatment: intramuscular epinephrine
Epinephrine auto-injector
Patient weight 10–25 kg: 0.15 mg
Patient weight >25 kg: 0.30 mg[#]
Epinephrine (1:1000)
0.01 mg·kg^{-1} per dose (max. 0.5 mg per dose) administered in the anterior lateral thigh
Epinephrine doses may need to be repeated every 5–15 minutes as needed
Adjunctive treatment
H_1 anti-histamine
Oral liquid diphenhydramine 1.25 mg·kg^{-1} (max. dose 50 mg)
Intravenous diphenhydramine 1–2 mg·kg^{-1} per dose (max. dose 50 mg)
Oral liquid cetirizine (6–24 months 2.5 mg; 2–5 years 5 mg; ⩾6 years 10 mg)
Bronchodilator (β_2-agonist): albuterol
Metered-dose inhaler (child 4–8 puffs; adult 8 puffs) [63]
Nebulised solution (child 1.5 mL; adult 3 mL)
Corticosteroids
Oral prednisone (1–2 mg·kg^{-1}, up to 60–80 mg)
Intravenous methylprednisolone (1 mg·kg^{-1}, up to 60–80 mg)
H_2 antagonist
Ranitidine 1–2 mg·kg^{-1} up to 75–150 mg oral or intravenous
For the hospitalised patient, administer other medications if needed as indicated
Supplemental oxygen, intravenous fluids, additional vasopressors, glucagon, atropine
Epinephrine is the first-line treatment in all cases of anaphylaxis
When respiratory symptoms are present in asthmatic patients due to suspected food-induced reaction, epinephrine should be administered as the initial treatment, before the use of a β_2-agonist

[#]: consider using 0.3 mg of epinephrine at a slightly lower weight in children with asthma [77].

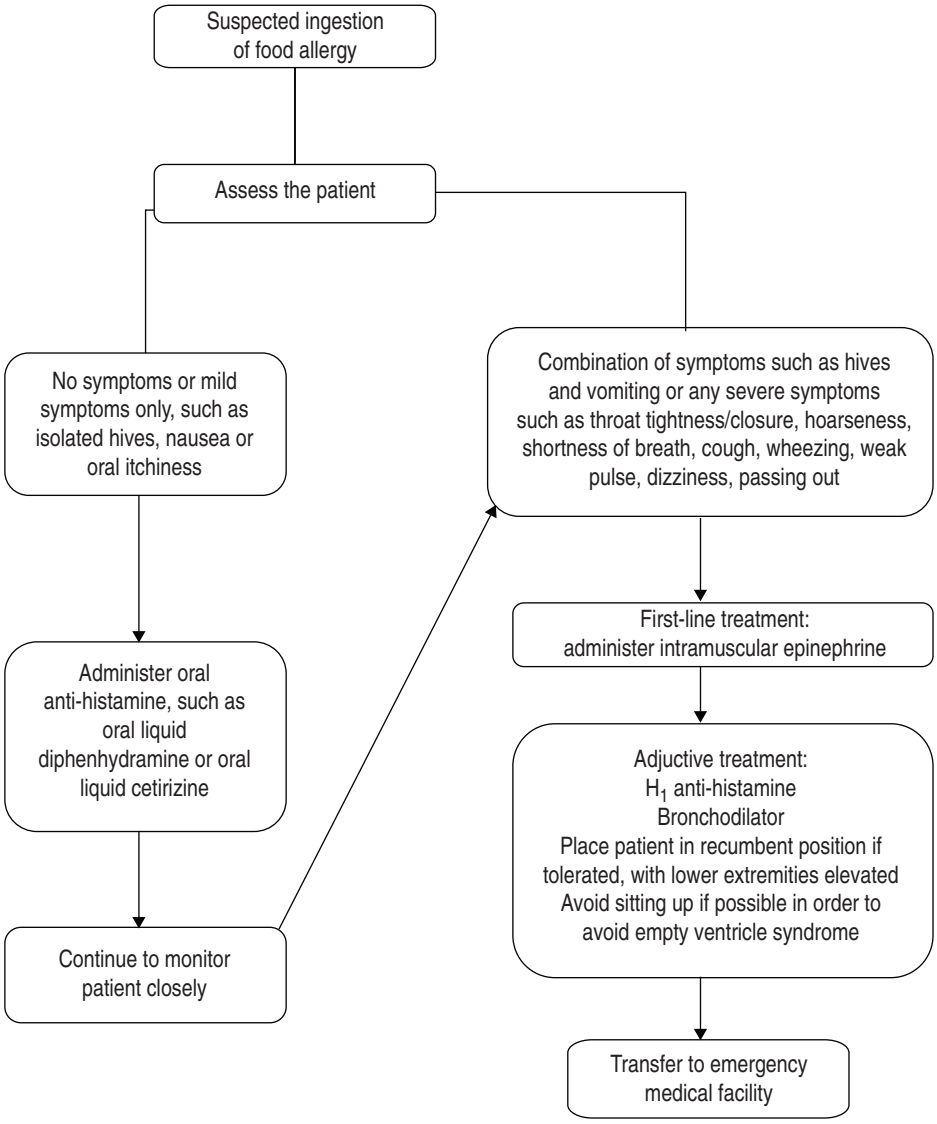
Suspected ingestion of food allergy
Assess the patient
No symptoms or mild symptoms only, such as isolated hives, nausea or oral itchiness
Combination of symptoms such as hives and vomiting or any severe symptoms such as throat tightness/closure, hoarseness, shortness of breath, cough, wheezing, weak pulse, dizziness, passing out
Administer oral anti-histamine, such as oral liquid diphenhydramine or oral liquid cetirizine
First-line treatment: administer intramuscular epinephrine
Adjuctive treatment: H_1 anti-histamine Bronchodilator Place patient in recumbent position if tolerated, with lower extremities elevated Avoid sitting up if possible in order to avoid empty ventricle syndrome
Continue to monitor patient closely
Transfer to emergency medical facility

Figure 1. Management of food-induced reaction in the field.

asthma or food allergy. If suspicion of food-induced anaphylaxis is high, injectable epinephrine is the treatment of choice; short-acting bronchodilators should not be relied upon in this situation.

A potential treatment which could target both food allergies and asthma is anti-IgE antibody. Omalizumab (Xolair®; Genentech, San Francisco, CA, USA) has already been approved by the US Food and Drug Administration for the treatment of patients aged $\geqslant$12 years with moderate-to-severe persistent allergic asthma [79]. Regarding the role of anti-IgE treatment in food allergy, LEUNG *et al.* [80] performed a double-blind randomised, dose-ranging trial of TNX-901, another anti-IgE formulation, in 84 patients with a history of peanut allergy. After 4 months of treatment, patients receiving the highest dose experienced significant decreases in symptoms with peanut challenge compared to the placebo group. The median threshold of sensitivity to peanut increased from 178 mg peanut protein (equivalent to one peanut) to almost nine peanuts (2.8 g). Although 25% of patients were able to tolerate over 20 peanuts post-treatment, another 25% failed to develop any change in tolerance to peanut indicating that the treatment response can be variable. A study using omalizumab was initiated for the treatment of peanut allergy, but discontinued for safety concerns related to the pre-treatment oral peanut challenge. However, data available from

the 14 patients who reached the study's primary end-point suggested an increase in tolerability to peanut flour in the omalizumab-treated *versus* placebo-treated subjects [81, 82]. Combination therapy of anti-IgE and allergen immunotherapy has been investigated as a method to decrease adverse reactions to immunotherapy in order to allow increased safety and efficacy [83], and there is currently an ongoing trial of omalizumab in conjunction with milk oral immunotherapy [81].

Conclusions

Coexisting food allergy and asthma place children at greater risk for morbidity and mortality. With increased awareness of the relationship between these two entities, the management of food allergy and asthma may improve. In addition, recognition of food-triggered asthma exacerbations is essential, and the goal should be preventing severe reactions such as anaphylaxis. An approach to managing this subset of patients which addresses the different facets of allergic disease can lead to optimal care.

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Statement of Interest

None declared.

References

1. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001; 107: 191–193.
2. Nagel G, Weinmayr G, Kleiner A, *et al.* Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. *Thorax* 2010; 65: 516–522.
3. Woods RK, Weiner J, Abramson M, *et al.* Patients' perceptions of food-induced asthma. *Aust N Z J Med* 1996; 26: 504–512.
4. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004; 114: 1282–1287.
5. Tepper RS, Llapur CJ, Conges MH, *et al.* Expired nitric oxide and airway reactivity in infants at risk for asthma. *J Allergy Clin Immunol* 2008; 122: 760–765.
6. Teague WG. Food allergen sensitization as a determinant of disturbed airway function in young infants: first step on the path to persistent asthma? *J Allergy Clin Immunol* 2008; 122: 766–767.
7. Tariq SM, Matthews SM, Hakim EA, *et al.* Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr Allergy Immunol* 2000; 11: 162–167.
8. Gaffin JM, Sheehan WJ, Morrill J, *et al.* Tree nut allergy, egg allergy, and asthma in children. *Clin Pediatr (Phila)* 2011; 50: 133–913.
9. Savage JH, Matsui EC, Skripak JM, *et al.* The natural history of egg allergy. *J Allergy Clin Immunol* 2007; 120: 1413–1417.
10. Priftis KN, Mermiri D, Papadopoulou A, *et al.* Asthma symptoms and bronchial reactivity in school children sensitized to food allergens in infancy. *J Asthma* 2008; 45: 590–595.
11. Jartti T, Kuusipalo H, Vuorinen T, *et al.* Allergic sensitization is associated with rhinovirus- but not other virus-induced wheezing in children. *Pediatr Allergy Immunol* 2010; 21: 1008–1014.
12. Wang J, Visness CM, Sampson HA. Food allergen sensitization in inner-city children with asthma. *J Allergy Clin Immunol* 2005; 115: 1076–1080.
13. Liu AH, Jaramillo R, Sicherer SH, *et al.* National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2010; 126: 798–806.
14. Roberts G, Patel N, Levi-Schaffer F, *et al.* Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. *J Allergy Clin Immunol* 2003; 112: 168–174.
15. Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. *Pediatr Pulmonol* 2007; 42: 489–495.
16. Schroeder A, Kumar R, Pongracic JA, *et al.* Food allergy is associated with an increased risk of asthma. *Clin Exp Allergy* 2009; 39: 261–270.
17. Malmberg LP, Saarinen KM, Pelkonen AS, *et al.* Cow's milk allergy as a predictor of bronchial hyperresponsiveness and airway inflammation at school age. *Clin Exp Allergy* 2010; 40: 1491–1497.

18. Krogulska A, Dynowski J, Wasowska-Królikowska K. Bronchial reactivity in schoolchildren allergic to food. *Ann Allergy Asthma Immunol* 2010; 105: 31–38.
19. James JM, Eigenmann PA, Eggleston PA, *et al.* Airway reactivity changes in asthmatic patients undergoing blinded food challenges. *Am J Respir Crit Care Med* 1996; 153: 597–603.
20. Büchele G, Genuneit J, Weinmayr G, *et al.* International variations in bronchial responsiveness in children: findings from ISAAC phase two. *Pediatr Pulmonol* 2010; 45: 796–806.
21. Thavagnanam S, Williamson G, Ennis M, *et al.* Does airway allergic inflammation pre-exist before late onset wheeze in children? *Pediatr Allergy Immunol* 2010; 21: 1002–1007.
22. Stern DA, Morgan WJ, Halonen M, *et al.* Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008; 372: 1058–1064.
23. Kulkami N, Ragazzo V, Costella S, *et al.* Eosinophilic airway inflammation is increased in children with asthma and food allergies. *Pediatr Allergy Immunol* 2011; 7: 1–6.
24. Hughes JL, Brown T, Edgar JD, *et al.* Peanut allergy and allergic airways inflammation. *Pediatr Allergy Immunol* 2010; 21: 1107–1113.
25. James JM. Respiratory manifestations of food allergy. *Pediatrics* 2003; 111: 1625–1630.
26. Salvatori N, Reccardini F, Convento M, *et al.* Asthma induced by inhalation of flour in adults with food allergy to wheat. *Clin Exp Allergy* 2008; 38: 1349–1356.
27. Gautrin D, Cartier A, Howse D, *et al.* Occupational asthma and allergy in snow crab processing in Newfoundland and Labrador. *Occup Environ Med* 2010; 67: 17–23.
28. Bock SA. Respiratory reactions induced by food challenges in children with pulmonary disease. *Pediatr Allergy Immunol* 1992; 3: 188–194.
29. James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994; 149: 59–64.
30. Saarinen KM, Pelkonen AS, Mäkelä MJ, *et al.* Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005; 116: 869–875.
31. Skripak JM, Matsui EC, Mudd K, *et al.* The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; 120: 1172–1177.
32. Rudd RA, Moorman JE. Asthma incidence: data from the National Health Interview Survey, 1980–1996. *J Asthma* 2007; 44: 65–70.
33. Centers for Disease Control and Prevention. Data and Surveillance. Asthma Surveillance Data. www.cdc.gov/asthma/asthmadata.htm Date last accessed: December 30, 2011. Date last updated: January 12, 2012.
34. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009; 124: 1549–1555.
35. Kumar R, Hui-Ju T, Hong X, *et al.* Race, ancestry, and development of food-allergen sensitization in early childhood. *Pediatrics* 2011; 128: e821–e829.
36. Akinbami L, Moorman JE, Garbe PL, *et al.* Status of childhood asthma in the United States, 1980–2007. *Pediatrics* 2009; 123: Suppl. 3, S131–S145.
37. Gupta RS, Springston EE, *et al.* The Prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; 128: e9–e17.
38. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence and trends of primary clinician-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol* 2011; 127: 623–630.
39. Sicherer SH, Muñoz-Furlong A, Godbold JH, *et al.* US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010; 125: 1322–1326.
40. Grundy J, Matthews S, Bateman B, *et al.* Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002; 110: 784–789.
41. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; 111: 1601–1608.
42. Yocum MW, Butterfield JH, Klein JS, *et al.* Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999; 104: 452–456.
43. Yunginger JW, Sweeney KG, Sturner WQ, *et al.* Fatal food-induced anaphylaxis. *JAMA* 1988; 260: 1450–1452.
44. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380–384.
45. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30: 1144–1150.
46. González-Pérez A, Aponte Z, Vidaurre CF, *et al.* Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol* 2010; 125: 1098–1104.
47. Iribarren C, Tolstykh IV, Miller MK, *et al.* Asthma and the prospective risk of anaphylactic shock and other allergy diagnoses in a large integrated health care delivery system. *Ann Allergy Asthma Immunol* 2010; 104: 371–377.
48. Varshney P, Steele PH, Vickery BP, *et al.* Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009; 124: 1351–1352.
49. DeBesche A. On asthma bronchiale in man provoked by cat, dog and different other animals. *Acta Med Scandinav* 1937; 92: 237–255.
50. Bernhisel-Broadbent J, Scanlon S, Sampson H. Fish hypersensitivity I. *In vitro* and oral challenge results in fish-allergic patients. *J Allergy Clin Immunol* 1992; 89: 730–737.

51. Salcedo G, Quirce S, Diaz-Perales A. Wheat allergens associated with baker's asthma. *J Investig Allergol Clin Immunol* 2011; 21: 81–92.
52. Perry TT, Conver-Walker MK, Pomes A, *et al.* Distribution of peanut allergen in the environment. *J Allergy Clin Immunol* 2004; 113: 973–976.
53. Comstock SS, Demera R, Vega LC, *et al.* Allergic reactions to peanuts, tree nuts, and seeds aboard commercial airliners. *Ann Allergy Asthma Immunol* 2008; 101: 51–56.
54. Maultiz RM, Pratt DS, Shocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979; 63: 433.
55. Kidd JM, Cohen SH, Sosman AJ, *et al.* Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; 71: 407–411.
56. Flannagan LM, Wolf BC. Sudden death associated with food and exercise. *J Forensic Sci* 2004; 49: 543–545.
57. Noma T, Yoshizawa I, Ogawa N, *et al.* Fatal buckwheat dependent exercise-induced anaphylaxis. *Asian Pac J Allergy Immunol* 2001; 19: 283–286.
58. Sicherer SH, Furlong TJ, Munoz-Furlong A, *et al.* A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 2001; 108: 128–132.
59. Uguz A, Lack G, Pumphrey R, *et al.* Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005; 35: 746–750.
60. Sicherer SH, Furlong TJ, DeSimone J, *et al.* The US Peanut and Tree Nut Allergy Registry: characteristics of reactions in schools and day care. *J Pediatr* 2001; 138: 560–565.
61. Furlong TJ, DeSimone J, Sicherer SH. Peanut and tree nut allergic reactions in restaurants or other food establishments. *J Allergy Clin Immunol* 2001; 108: 867–870.
62. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age 7 years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95: 1179–1190.
63. Nicolaou N, Poorafshar M, Murray C, *et al.* Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010; 125: 191–197.
64. Asarnoj A, Movérare R, Ostblom E, *et al.* IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. *Allergy* 2010; 65: 1189–1195.
65. Fernandes J, Reshef A, Patton L, *et al.* Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews. *Clin Exp Allergy* 2003; 33: 956–961.
66. Rosenstreich DL, Eggleston P, Kattan M, *et al.* The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997; 336: 1356–1363.
67. Pénard-Morand C, Raherison C, Kopferschmitt C, *et al.* Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy* 2005; 60: 1165–1171.
68. Valenta R, Kraft D. Type 1 allergic reactions to plan-derived food: a consequence of primary sensitization to pollen allergens. *J Allergy Clin Immunol* 1996; 97: 893.
69. Ortolani C, Pastorello EA, Farioli L, *et al.* IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993; 71: 470.
70. Fernandez-Rivas M, van Ree R, Cuevas M. Allergy to Rosaceae fruits without related pollinosis. *J Allergy Clin Immunol* 1997; 100: 728.
71. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010; 376: 814–825.
72. Baena-Cagnani CE, Badellino HA. Diagnosis of allergy and asthma in childhood. *Curr Allergy Asthma Rep* 2011; 11: 71–77.
73. National Institutes of Health, National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 07-4051. 2007.
74. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2008 update. www.ginasthma.com.
75. Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol* 2010; 126: 1105–1118.
76. Maloney JM, Nowak-Wegrzyn A, Wang J. Children in the inner city of New York have high rates of food allergy and IgE sensitization to common foods. *J Allergy Clin Immunol* 2011; 128: 214–215.
77. Simons FE, Roberts JR, Gu X, *et al.* Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998; 101: 33–37.
78. National Asthma Education and Prevention Program. Management of Asthma Exacerbation: School Treatment. www.ashaweb.org Date last updated: August, 2011. Date last accessed: October 17, 2011.
79. Milgrom H, Fick RB, Su JQ, *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody: rhuMAb-E25 Study Group. *N Engl J Med* 1999; 341: 1966–1973.
80. Leung DY, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348: 986–993.

81. Sampson HA, Leung DY, Burks AW, *et al.* A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011; 127: 1309–1310.
82. Casale TB, Busse WW, Kline JN, *et al.* Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; 117: 134–140.
83. ClinicalTrials.gov. National Institute of Allergy and Infectious Diseases (NIAID). OIT and Xolair® (Omalizumab) in Cow's Milk Allergy. NCT01157117. http://clinicaltrials.gov/ct2/show/NCT01157117.

Chapter 7

The burden of paediatric asthma: economic and familiar

Francis J. Gilchrist and Warren Lenney

SUMMARY: Asthma is the commonest chronic illness of childhood and has a huge, yet variable, burden that impacts on the child, their family, the healthcare system and society as a whole. The economic burden can be broken down to assess the direct and the indirect costs of the disease. Many studies have been undertaken in numerous countries and the burden clearly differs depending on the healthcare system in which the child is cared for, the severity of the child's disease, the social status of the child's family and a number of other factors included in some of the studies. For the affected child there are physical, social and psychological effects, which have a detrimental effect on their quality of life. The lives of their parents and siblings are also affected. Despite increasing medication costs and an increase in the worldwide prevalence of paediatric asthma, there is evidence that carefully planned asthma management programmes can reduce the burden on individual patients and the wider society. Improved understanding of the various aspects of the burden of paediatric asthma, along with help to develop these management programmes and target them to the needs of particular communities, could maximise these positive results. The single most important factor in reducing the burden of paediatric asthma is to improve asthma control; therefore, we need to be vigilant in optimising the care of children with asthma at all times.

KEYWORDS: Asthma, children, paediatrics

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Paediatric asthma remains one of the commonest chronic illnesses of children and is a serious global health problem with a wide ranging and significant burden. This burden includes the economic impact of the disease, which not only affects the patient but also the patient's family, the healthcare system in which the family lives, and indeed society as a whole. There are also more subjective, but equally important, social effects on the child and their family [1]. As health economic outcomes are increasingly being used by healthcare providers to guide decision making, the quantification of the economic burden or "cost-of-illness" is becoming increasingly more

important [2]. The economic burden can be divided into direct costs, which are wholly generated within the healthcare system, and indirect costs that are associated with the loss of economic productivity. Both aspects are relatively easy to quantify, although some healthcare systems and published medical papers concentrate only on the direct costs. The psychological and social effects that paediatric asthma has on family life can be evaluated as an indirect cost; however, these are much more difficult to quantify and to allocate an appropriate and accurate economic value.

Prevalence of paediatric asthma

When analysing the burden of any illness within a population it is important to understand and assess its global prevalence. The largest study to have provided data on the global prevalence of paediatric asthma was the International Study of Asthma and Allergies in Childhood (ISAAC) [3]. ISAAC Phase One surveyed the prevalence of self-reported asthma symptoms in adolescents (children aged 13–14 years) and parent-reported asthma symptoms in children aged 6–7 years during 1994 to 1995. It included 155 centres across 56 countries with approximately 3,000 children per centre. The global prevalence for ''wheeze in the last 12 months'' was 11.8% in children (range 4.1–32.1%) and 13.8% in adolescents (range 2.1–32.2%). The global prevalence for ''asthma ever'' was 10.2% in children (range 1.4–27.1%) and 11.3% in adolescents (range 1.6–28.2%). Prevalence tended to be higher in English speaking countries and in Latin America. The reason for the variation in paediatric asthma prevalence is not clearly understood but it may be linked to allergen exposure, other childhood respiratory illnesses, dietary and environmental lifestyles, and socioeconomic differences [4].

ISAAC Phase Three repeated Phase One in 106 centres across 56 countries for adolescents aged 13–14 years and 66 centres across 37 countries for children aged 6–7 years (fig. 1) [6]. It was conducted from 2001 to 2003 and its aim was to assess changes over time in the worldwide prevalence of asthma symptoms. ISAAC Phase Three confirmed that the global burden of paediatric asthma was continuing to increase with small increases in the overall prevalence of ''wheeze in the last 12 months'' (+0.06% per year in adolescents and +0.13% per year in children) and more significant increases in the prevalence of ''asthma ever'' (+0.28% per year in adolescents and +0.18% per year in children). Despite these increases, the international differences in asthma symptom prevalence had reduced. This is due to the decreased prevalence in English speaking countries and Western Europe and an increased prevalence in regions where prevalence was previously low (fig. 2).

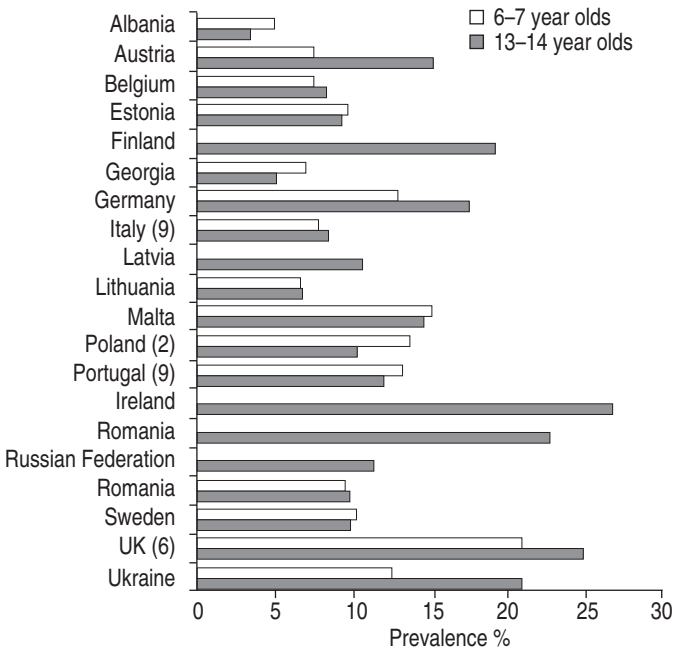

Figure 1. Prevalence of asthma symptoms in children aged 6–7 years and 13–14 years in Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC), 2001–2003. Data collected from more than one centre is presented in brackets. Reproduced and modified from [5] with permission from the publisher.

Economic burden

Direct costs

Direct costs include the specific medical costs associated with the disease, such as emergency department

attendances, primary and secondary care physician visits, nursing services, in-patient care, drugs and devices, diagnostic tests, research, and education [7]. The direct costs also include the non-medical costs associated with the disease, such as transportation of the child and family to and from medical appointments, or hospital admissions, together with household modifications to reduce allergic contact and hence symptoms associated with house dust mite, pets, feathers and other common allergens. Most studies have shown the direct costs of paediatric asthma to exceed the indirect costs, accounting for 51–88% of the total costs [8–11].

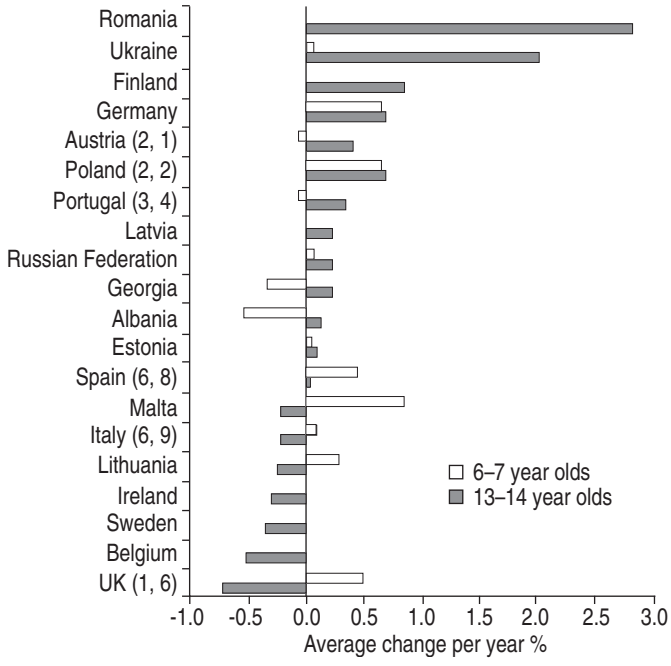

Figure 2. Annual change in prevalence of asthma in children between International Study of Asthma and Allergies in Childhood (ISAAC) Phase One (1994–1995) and Phase Three (2001–2003). Data collected from more than one centre during each phase is presented in brackets. Reproduced and modified from [5] with permission from the publisher.

Hospital admission

Although only a minority of children with asthma are admitted to hospital, this usually accounts for the largest component of the healthcare costs. In a prospective Canadian study, only 9% of asthmatic children aged 4–14 years required hospitalisation; however, this accounted for 77% of the annual cost to the Ministry of Health [10]. Another prospective study assessing the economic impact of preschool wheeze in the UK found that following an initial admission with wheeze or asthma the average number of in-patient days was 0.65 per patient per year. This represented 57% of the total healthcare costs [9]. Due to the disproportionate costs of in-patient care this is often the primary target when trying to reduce the economic impact of paediatric asthma. This was highlighted in a study undertaken in Switzerland in which a lower rate of hospitalisation (0.3 hospital days per patient per year) resulted in the in-patient care accounting for only 38% of the total direct costs [12]. Due to increased rates of hospitalisation and re-hospitalisation, it was observed that younger children consume up to three times more in-patient resources per capita than older children [13].

Medication costs

After in-patient care, the next largest single component of direct cost is medications, which account for 22–43% of the total direct cost [10, 12, 14]. This is despite the cost of anti-asthma medications for children being less than half the cost of those prescribed for adults [14]. Other direct costs are similar in adults and children. As expected, children with more severe asthma use increasing amounts of expensive medications, which are escalating in cost and, therefore, have higher medication costs [15]. Table 1 shows the estimated annual costs of different asthma therapies for a 5 year old and a 15 year old, these are approximate values based on average doses [16]. Reducing the medication costs is another key target when trying to reduce the financial burden of paediatric asthma. As those with good asthma control have lower medication costs, this is also achieved by improving asthma control.

Physician visits

Primary care physicians are the commonest contact for children with asthma and account for 11–19% of the direct costs [9, 10]. In preschool children with a previous in-patient admission, the

Table 1. Estimated annual costs of various anti-asthma treatments

	5-year-old child[#]	15-year-old adolescent
Short-acting β_2-agonist	£17.30 (based on six inhalers per year)	£34.60 (based on 12 inhalers per year)
Inhaled corticosteroid	£30.80 (beclometasone 200 mcg·day^{-1})	£134.60 (beclometasone 800 mcg·day^{-1})
Inhaled combination therapy	£70.70 (fluticasone/Salmeterol 200 mcg·day^{-1})	£276.40 (fluticasone/salmeterol 500 mcg·day^{-1})
LTRA	£308.30 (montelukast 4 mg·day^{-1})	£323.60 (montelukast 10 mg·day^{-1})
Omalizumab	NA	£3,074–£12,295[¶]

Costs are presented in GBP. LTRA: leukotriene receptor antagonist; NA: not applicable. [#]: omalizumab (Xolair®; Genentech, San Francisco, CA, USA) is not licensed in this age. [¶]: dependent on weight and total immunoglobulin E. Data taken from [16].

average number of visits to the primary care physician was 4.8 per year [9]. In children aged 4–14 years with asthma, 80% had visited their primary care physician in the last year and 11% had done so on six or more occasions [10]. Visits to secondary care physicians and the emergency department are less frequent and account for 11% and 1–2% of direct costs, respectively [9, 10].

Family borne costs

The family of an asthmatic child often have to endure part of the financial burden. Their expenses may include travel to hospital or physician appointments, purchase of nonprescription medication and the payment for food and drink when away from home. This cost has been estimated as 1–6% of the total direct costs [9, 10].

Indirect costs

Indirect costs refer to the value of the resources that are lost due to an absence from work by the carer, and loss of schooling by the child. Although a rare event, should a child die due to an asthma exacerbation the life-long potential earnings loss can be calculated and expressed as an indirect cost. The indirect costs associated with paediatric asthma are significant, with up to 54% of children with asthma having missed school in the previous year due to asthma symptoms/exacerbations and 9% missing more than 2 weeks of schooling per year [17]. In many societies today both parents need to work away from the family home. This means school absenteeism can also results in decreased parental productivity due to parents taking carers leave from work. In one large survey 39% of parents reported having to miss work in the previous year because of their child's asthma (mean 2.6 days per year) [17]. As highlighted recently, by the Royal marriage of HRH Prince William of Wales and Katherine Middleton in the UK, if large numbers of people are absent from work for even a single extra day per year it can have a significant effect on the national economy (Confederation of British industry (CBI), London, UK, www.cbi.org.uk). Depending on how they are calculated, indirect costs have been found to account for between 12% and 49% of the total cost of paediatric asthma [10, 11]. The adverse effect that a disease has on the quality of life (QoL) for the patient and the family members can also be viewed as an indirect cost. Although the effect on QoL can be quantified it is difficult to translate this into a financial value. The indirect costs differ between adults and children as children do not lose working days, although their parents might.

Methodology for assessing cost of illness

There are two methods for measuring the cost of illness. Prevalence studies measure the cost of an illness in a population over a defined period of time, the period of time is usually measured as one

calendar year. Both incidence and prevalence cases are included in prevalence studies. Incidence cost-of-illness studies estimate the lifetime costs for a specific disease for all patients with the onset of that disease in a given calendar year [18].

Cost-of-illness estimations for paediatric asthma

A large number of studies have evaluated the economic burden of paediatric asthma in particular populations at various times. These are difficult to compare due to the different definitions of asthma that have been used, the different methods of estimating direct and indirect costs, and the use of different national monetary currencies. The costs are also affected by inflation and the variable exchange rates between different currencies; facts particularly recognised in the present global financial situation. One of the most useful papers covering this topic is a prevalence study by VAN DEN AKKER-VAN MARLE *et al.* [2], which estimated the cost of illness for asthma in children under the age of 15 years in the 25 European Union member states in 2004, allowing comparisons to be made between the countries. This was undertaken using relevant published data with appropriate conversions, inflation and comparative financial estimations. The estimated average annual cost of paediatric asthma per child was €613. The minimum estimate was €142 in Estonia with the maximum estimate being €1,529 in Hungary. This is interesting as the country with the highest costs per patient is not the country with the highest medical expenditure. Direct costs accounted for between 57% and 94% of the total costs. For each country the cost per child was multiplied by the prevalence giving a total cost for each European country. The estimated total cost of childhood asthma for the 25 European Union member states in 2004 was €3 billion. If the definition of asthma was changed to ''wheeze'' then the estimate rose to €5.2 billion.

Using data from the Medical Expenditure Panel Survey, the economic burden of asthma was estimated in children aged 5–17 years in the USA [11]. The direct medical expenditure, which included payments for medication, hospital in-patient stays, out-patient attendances, emergency room visits and office-based visits, was estimated at $1.01 billion, a total of $401 per child with asthma. The indirect costs were estimated as $983.8 million, which was $390 per child with asthma. This included $719.1 million for the loss of productivity associated with parents taking time off work to care for their asthmatic child, with some $264.7 million being estimated for the loss of earnings of the 211 school aged children who died of asthma in the year in which the data were collected. The number of school days missed by children with asthma due to asthma symptoms and or exacerbations was 6.3 million (2.48 days per child). The total estimated economic impact of asthma in school aged children in the USA was estimated at $1.99 billion ($791 per child with asthma). This value fits surprisingly well with the estimated financial burden of paediatric asthma in European countries.

Predictors for the cost of illness

On an individual patient basis the presence of certain factors has been shown to be associated with increased costs. As expected, those with poorly controlled asthma (high number of symptom days) have a higher annual cost of illness [19]. As discussed earlier, this relates to more frequent and lengthier stays in hospital, higher medication costs and more contact with primary and secondary care physicians. Conversely, as asthma control improves the cost of illness reduces. Therefore, improving asthma control is the key to reducing the economic burden of paediatric asthma. The forced expiratory volume in 1 second (FEV_1) does not correlate well with the cost of illness for paediatric asthma, highlighting the proportion of children with mild-to-moderate asthma that have normal lung function between exacerbations.

Other factors associated with a higher cost of illness are young ages (particularly those less than 5 years of age), low-income status and longer duration of asthma [19]. In younger children this is reflected in the increased incidences of hospitalisations and also the difficulties in determining

whether the diagnosis is asthma- or a viral-induced wheezing, which responds less well to inhaled corticosteroids (ICS) [13]. Children from low-income families are known to have reduced access to healthcare and are more likely to be exposed to tobacco smoke [20]. This results in poorer asthma control. More frequent asthma exacerbations increases the likelihood of an admission to hospital, thereby increasing the cost of treatment. Patients with a longer duration of asthma are more likely to have severe disease than those with intermittent symptoms, thereby raising treatment costs.

The social burden of paediatric asthma

Social burden on the child

Paediatric asthma has a profound social burden affecting not only the child but also the family. The social and emotional burden that asthma has on the child can be subdivided into four main categories: social and leisure pursuits, schooling, practical aspects of daily life, and emotional effects [21].

Social and leisure pursuits

The extent to which asthma prevents children from participating in play and recreational activities depends on how well their symptoms are controlled. Despite this, a large survey of children with asthma found 62% of children were limited in at least one of the following activities: playing organised sports, outdoor activities, owning pets, sleeping without nocturnal waking, going out/playing with friends, doing things with their family, progressing well educationally in school, and participating in school activities [17]. Another study found 39% of children with asthma needed to miss sport because of their asthma and 22% had been advised to avoid certain sports altogether [22]. Frequent hospital admissions and visits to the primary care physician or paediatric outpatient clinic also have a social burden on the child, because the child misses out on other activities, and a psychological effect, especially when the child is unwell.

Schooling

Asthma symptoms result in school absenteeism in 35–66% of children with asthma [17, 23–26]. A systematic review in 2004 included 29 published articles and found the absence rates for any cause among children with asthma ranged from 7.7 to 40 days per year and absence as a result of asthma symptoms/exacerbations ranging from 2.1 to 14.8 days per year [27]. Those with more severe asthma had a higher absence rate and often missed more than 30 days per year [28]. Children with asthma strived to participate fully at school and felt that this was possible if they received the necessary support, especially from adults at their school [29]. However, they did have anxiety when they missed school and may have had difficulty in catching up with school work when they returned to school. Given the high absence rates it is logical to assume that academic performance would definitely be affected. However, studies have failed to show a significant difference between the academic performance of children with asthma and those without [24, 30–33]. Interestingly, children with asthma whose parents are affected by a chronic disease have more time off school than asthmatic children whose parents are not affected by a chronic disease, highlighting the complex balance of factors that are likely to affect children with a disease such as asthma [26].

Practical aspects of daily life

Night-time symptoms cause disrupted sleep and contribute to daytime tiredness and reduced school performance, with 63% of asthmatic children having, at some time, been woken by cough or wheeze [23]. In one study this occurred in the previous week in 30% of the children [34]. Children may need to avoid certain environments (*e.g.* cold, smoky, dusty *etc.*) or avoid contact

with certain animals or foods. All such factors, in addition to the need to take regular and or intermittent medications, separate a child with asthma from their peers. This is really important as peer group pressure is strong throughout childhood and is particularly so in the teenage years. There is a pressure for adolescents to conform to the ''normal'' behaviour of their friends and deviation from this behaviour, because of their asthma, is difficult to accept. This undoubtedly has a negative effect on adherence to asthma medications.

Adherence issues are well described in the management of chronic disease [35, 36], and much has been written on poor adherence to asthma medications, particularly in teenagers [37]. Lack of regular usage of preventative therapies, such as ICS, are recognised as causes of poor control, increased exacerbations and significant increases in the overall financial and social burden that asthma imposes on its sufferers and the healthcare system.

Emotional effects

As with any chronic disease, asthma has significant emotional effects on the child, which in turn impacts on symptom perception and compliance with medications. The symptoms of asthma include cough, wheeze and shortness of breath. As doctors, nurses and carers we use these words all the time but need to remember that they are unpleasant and distressing for the child. It should also be remembered that parents tend to underestimate their child's asthma severity and overestimate asthma control [38]. With regard to their asthma symptoms, 30% of children with asthma feel fearful or angry, 20% have felt depressed and 19% state they are embarrassed [17].

Social burden on the family

In addition to having an impact on the child's own life, asthma also impacts on the lives of their parents and siblings. The whole family, especially siblings, may have to limit certain social and leisure pursuits due to the possible effects these may have on the child with asthma. It may not just be the child with asthma who loses sleep as other members of the family may endure sleepless nights when the child with asthma is unwell. Parents report being constantly worried about the possibility of asthma attacks, even when their child's symptoms are well controlled [39]. Parents are also concerned about the effects of long-term medication, particularly regarding the possible effects of ICS on growth [40]. Over one-third of parents reported that their child's asthma put a strain on the relationship with their partner [41]. In some cases, parental anxiety can lead to over protectiveness or a failure to set appropriate behavioural boundaries [42]. Parents of children with asthma also report feeling guilty regarding their child's diagnosis, especially if they are atopic or asthmatic themselves [21]. It is commonly perceived that parents spend less time with their child's healthy sibling than their child with asthma, potentially affecting the relationship the healthy sibling has with the parents and the child with asthma. Although this can lead to guilt and resentment, most children are extremely understanding and are usually helpful towards their sibling with asthma [41]. From a practical perspective, parents have to miss work to care for their child, either when they are unwell or in order to take them to the hospital or primary care physician for regular, as well as unscheduled, visits. Despite this social burden on the family it is unusual to hear parents of children with asthma complain about these issues. They focus much more on the effect asthma has on their child.

Quality of life for the child with asthma

One way of quantifying the social effect of asthma is to measure the child's QoL. Many studies, using a wide range of QoL tools, have consistently shown that children with asthma have a poorer QoL than their healthy peers. A cohort study showed impaired QoL for eight of the 11 scales of the Child Health Questionnaire in 61 symptomatic, asthmatic children when compared with 1,967 nonasthmatic children [43]. The How Are You? QoL questionnaire and the Child Attitude

Towards Illness Scale were used to demonstrate reduced participation and worse quality of performance for physical and social activities, and more negative feelings towards limitations in social activities in 228 children with asthma compared with 296 of their healthy peers [44]. As may be expected, the more severe the child's asthma, the more the QoL is affected. This has been demonstrated in a recent study in which the Paediatric Asthma Quality of Life Questionnaire scores were significantly lower in children with problematic severe asthma compared with age-matched children with controlled asthma [45].

Quality of life for the caregiver of a child with asthma

As with the children, the social effect that a child's asthma has on the parent can be quantified using QoL tools. The Paediatric Asthma Caregivers Quality of Life Questionnaire was developed for this specific group of carers, and has been used to demonstrate a decreased QoL in the parents of children with asthma [46]. As was found in the children with asthma, the effect is greater in the carer when the child's asthma is poorly controlled [47]. Similar findings have been demonstrated using the more recent Family Impact of Childhood Bronchial Asthma questionnaire [48]. When parent-reported QoL is compared with child-reported QoL the correlation improves as the age of the child increases [49].

Reducing the burden of paediatric asthma

During a time in which the incidence of asthma and the cost of anti-asthma medications are increasing, it seems an almost impossible goal to decrease the burden of paediatric asthma. However, various locations around the world have been successful in achieving this through the implementation of asthma programmes that target improved asthma control, thereby reducing the need for hospitalisation, the use of medication, and the number of physician visits. Some of these programmes are for defined small populations, such as children with asthma in specific affluent poor urban communities [50, 51], whilst others are national programmes for all adults and children with asthma [52–55].

The best example of a large scale programme is the National Asthma Programme of Finland, which was undertaken from 1994–2004 [55]. In 1993 the Ministry of Social Affairs in Finland recognised the importance of asthma and appointed a working group to design a national programme, the main aim of the group was to decrease the burden of asthma for individual patients and society as a whole. The working group proposed a series of measures to achieve this goal [56]. These measures included: early diagnosis and active treatment; guided, self-management as the primary form of treatment; a reduction in respiratory irritants (*e.g.* tobacco smoke); patient education and rehabilitation, combined with normal treatment; increased knowledge of asthma in key groups; and the promotion of scientific research. The programme was run by a nongovernmental organisation and employed one pulmonologist. The direct cost of the programme was €650,000. The programme obtained broad commitment from the Finnish healthcare system and key to its success was a network of local asthma coordinators (200 asthma physicians and 580 asthma nurses), of which at least one could be found in each of the 271 Finnish healthcare centres [55]. These coordinators were responsible for regional cooperation with referral and treatment networks and guidelines. Nearly all Finnish pharmacies were included in the programme and support was also given by patient organisations and pharmaceutical companies. The Finnish National Asthma Programme was extremely successful. Between 1993 and 2003 the number of asthmatic patients increased in Finland from 135,363 to 207,757 but the number of hospitalisation days due to asthma fell from 110,000 to 51,000 and the number of asthmatic patients of working age claiming disability pension from the Social Insurance Institution decreased from 7,212 to 1,741. This resulted in a decrease in the total cost of asthma care in Finland from €218 million to €213.5 million and the cost per patient, per year fell from €1,611 to €1,031. The success of this programme highlighted that the burden of asthma can be reduced if the necessary planning and support is put into place.

Conclusions

Paediatric asthma is a significant burden affecting the child, their family, the healthcare system and wider society. The economic burden is huge but despite being affected by a large number of factors it is remarkably similar across Europe and the USA. The main components of the economic burden are the costs of in-patient care, medications and physician visits, all of which can be reduced by improving asthma control. Of equal importance is the social burden that asthma has on the affected child and family. Asthma can affect all aspects of the child's life and often results in a reduced QoL for both the child and their family. Again there is clear evidence that improving asthma control can reduce the social burden for all affected. The burden of paediatric asthma is a real issue and given the increasing prevalence of paediatric asthma, especially in developing countries, it is likely to increase. This can only be reversed by the implementation of carefully designed asthma management programmes that are implemented on a national or international scale.

Statement of Interest

None declared.

References

1. Bousquet PJ, Daures J-P. Modelization of cost assessment in childhood asthma is essential for policy makers. *Allergy* 2005; 60: 135–137.
2. van den Akker-van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: assessing the burden to society of asthma in children in the European Union. *Allergy* 2005; 60: 140–149.
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12: 315–335.
4. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351: 1225–1232.
5. World Health Organization Europe. Prevalence of asthma and allergies in children. European Environment and Health Information System (ENHIS) Fact sheet no. 3.1. May 2007. CODE: RPG3_Air_E1. Available from: www.euro.who.int/__data/assets/pdf_file/0012/96996/3.1.pdf
6. Pearce N, Aït-Khaled N, Beasley R, *et al.* Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62: 758–766.
7. Bahadori K, Doyle-Waters MM, Marra C, *et al.* Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009; 9: 24.
8. Schramm B, Ehlken B, Smala A, *et al.* Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J* 2003; 21: 116–122.
9. Stevens CA, Turner D, Kuehni CE, *et al.* The economic impact of preschool asthma and wheeze. *Eur Respir J* 2003; 21: 1000–1006.
10. Ungar WJ, Coyte PC. Prospective study of the patient-level cost of asthma care in children. *Pediatr Pulmonol* 2001; 32: 101–108.
11. Wang LY, Zhong Y, Wheeler L. Direct and indirect costs of asthma in school-age children. *Prev Chronic Dis* 2005; 2: A11.
12. Szucs TD, Anderhub H, Rutishauser M. The economic burden of asthma: direct and indirect costs in Switzerland. *Eur Respir J* 1999; 13: 281–286.
13. Valovirta E, Kocevar VS, Kaila M, *et al.* Inpatient resource utilisation in younger (2–5 yrs) and older (6–14 yrs) asthmatic children in Finland. *Eur Respir J* 2002; 20: 397–402.
14. Schramm B, Ehlken B, Smala A, *et al.* Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J* 2003; 21: 116–122.
15. Mossing R, Nielsen GD. De samfundsokonomiske omkostninger ved astma i Danmark i 2000. [Cost-of-illness of asthma in Denmark in the year 2000.] *Ugeskr Laeg* 2003; 165: 2646–2649.
16. Paediatric Formulary Committee, ed. British National Formulae for Children 2010–2011. London, BMJ Group, Pharmaceutical Press and RCPCH publications, 2010.
17. Children and Asthma in America: Executive Survey. 2004. Research Triangle Park, GlaxoSmithKline. Available from: www.srbi.com/CA_exec_sum_9202.pdf
18. Gergen PJ. Understanding the economic burden of asthma. *J Allergy Clin Immunol* 2001; 107: Suppl. 5, S445–S448.
19. Gendo K, Sullivan SD, Lozano P, *et al.* Resource costs for asthma-related care among paediatric patients in managed care. *Ann Allergy Asthma Immunol* 2003; 91: 251–257.

20. Lenney W, Enderby B. "Blowing in the wind": a review of teenage smoking. *Arch Dis Child* 2008; 93: 72–75.
21. Nocon A. Social and emotional impact of childhood asthma. *Arch Dis Child* 1991; 66: 458–460.
22. Coughlin SP. Sport and the asthmatic child: a study of exercise-induced asthma and the resultant handicap. *J R Coll Gen Pract* 1988; 38: 253–255.
23. Austin JB, Selvaraj S, Russell G. Childhood asthma in the Highlands of Scotland-morbidity and school absence. *Scott Med J* 2004; 49: 18–21.
24. Anderson HR, Bailey PA, Cooper JS, *et al.* Morbidity and school absence caused by asthma and wheezing illness. *Arch Dis Child* 1983; 58: 777–784.
25. Hill RA, Standen PJ, Tattersfield AE. Asthma, wheezing, and school absence in primary schools. *Arch Dis Child* 1989; 64: 246–251.
26. Lipstein EA, Perrin JM, Kuhlthau KA. School absenteeism, health status, and health care utilization among children with asthma: associations with parental chronic disease. *Padiatrics* 2009; 123: e60–e66.
27. Milton B, Whitehead M, Holland P, *et al.* The social and economic consequences of childhood asthma across the lifecourse: a systematic review. *Child Care Health Dev* 2004; 30: 711–728.
28. Lenney W. The burden of paediatric asthma. *Pediatr Pulmonol Suppl* 1997; 15: 13–16.
29. Rydström I, Englund AC, Sandman PO. Being a child with asthma. *Pediatr Nurs* 1999; 25: 589–590, 593–596.
30. Padur JS, Rapoff MA, Houston BK, *et al.* Psychosocial adjustment and the role of functional status for children with asthma. *J Asthma* 1995; 32: 345–353.
31. Silverstein MD, Mair JE, Katusic SK, *et al.* School attendance and school performance: a population-based study of children with asthma. *J Pediatr* 2001; 139: 278–283.
32. Peckham C, Butler N. A national study of asthma in childhood. *J Epidemiol Community Health* 1978; 32: 79–85.
33. Rietveld S, Colland VT. The impact of severe asthma on schoolchildren. *J Asthma* 1999; 36: 409–417.
34. Lenney W. Burden of paediatric asthma. *Eur Respir Rev* 1994; 4: 49–62.
35. Ingerski LM, Hente EA, Modi AC, *et al.* Electronic measurement of medication adherence in paediatric chronic illness: a review of measures. *J Pediatr* 2011; 159: 528–534.
36. Chacko A, Newcorn JH, Feirsen N, *et al.* Improving medication adherence in chronic paediatric health conditions: a focus on ADHD in youth. *Curr Pharm Des* 2010; 16: 2416–2423.
37. Drotar D, Bonner MS. Influences on adherence to paediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr* 2009; 30: 574–582.
38. Carroll WD, Wildhaber J, Brand PLP. Parent misperception of control in childhood/adolescent asthma: the room to breathe survey. *Eur Respir J* 2012; 39: 90–96.
39. Quinn CM. Children's asthma: new approaches, new understandings. *Ann Allergy* 1988; 60: 283–292.
40. Townsend M, Feeny DH, Guyatt GH, *et al.* Evaluation of the burden of illness for paediatric asthmatic patients and their parents. *Ann Allergy* 1991; 67: 403–408.
41. Donnelly JE, Donnelly WJ, Thong YH. Parental perceptions and attitudes toward asthma and its treatment: a controlled study. *Soc Sci Med* 1987; 24: 431–437.
42. Lask B. Emotional considerations in wheezy children. *J R Soc Med* 1979; 72: 56–59.
43. Merikallio VJ, Mustalahti K, Remes ST, *et al.* Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005; 16: 332–340.
44. le Coq EM, Colland VT, Boeke AJ, *et al.* Reproducibility, construct validity, and responsiveness of the "How Are You?" (HAY), a self-report quality of life questionnaire for children with asthma. *J Asthma* 2000; 37: 43–58.
45. Nordlund B, Konradsen JR, Pedroletti C, *et al.* The clinical benefit of evaluating health-related quality-of-life in children with problematic severe asthma. *Acta Paediatr* 2011; 100: 1454–1460.
46. Juniper EF, Guyatt GH, Feeny DH, *et al.* Measuring quality of life in the parents of children with asthma. *Qual Life Res* 1996; 5: 27–34.
47. Halterman JS, Yoos HL, Conn KM, *et al.* The impact of childhood asthma on parental quality of life. *J Asthma* 2004; 41: 645–653.
48. Forns D, Prat R, Tauler E. Evaluation of quality of life among the caregivers of asthmatic children: the new IFABI-R questionnaire. *Allergol Immunopathol (Madr)* 2011; 39: 32–38.
49. Annett RD, Bender BG, DuHamel TR, *et al.* Factors influencing parent reports on quality of life for children with asthma. *J Asthma* 2003; 40: 577–587.
50. Cloutier MM, Grosse SD, Wakefield DB, *et al.* The economic impact of an urban asthma management program. *Am J Manag Care* 2009; 15: 345–351.
51. Meng Y-Y, Pourat N, Cosway R, *et al.* Estimated cost impacts of law to expand coverage for self-management education to children with asthma in California. *J Asthma* 2010; 47: 581–586.
52. Franco R, Santos AC, do Nascimento HF, *et al.* Cost-effectiveness analysis of a state funded programme for control of severe asthma. *BMC Public Health* 2007; 7: 82.
53. Kupczyk M, Haahtela T, Cruz AA, *et al.* Reduction of asthma burden is possible through National Asthma Plans. *Allergy* 2010; 65: 415–419.

54. Stelmach W, Majak P, Jerzynska J, *et al.* Early effects of Asthma Prevention Program on asthma diagnosis and hospitalization in urban population of Poland. *Allergy* 2005; 60: 606–610.
55. Haahtela T, Tuomisto LE, Pietinalho A, *et al.* A 10 year asthma programme in Finland: major change for the better. *Thorax* 2006; 61: 663–670.
56. Haahtela T, Laitinen LA. Asthma programme in Finland 1994–2004. Report of a working Group. *Clin Exp Allergy* 1996; 26: Suppl. 1, i–ii, 1–24.

Chapter 8

Lung development and the role of asthma and allergy

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SUMMARY: Lung function, asthma and allergy are complexly involved in children and adults; however, the role of lung function development in relation to asthma and allergy is not clear. Does reduced lung function in early post-uterine life infer a (causal) risk for later asthma, or is it simply a marker for ongoing disease development? If so, what is the association between reduced lung function, allergic sensitisation, allergen exposure and viral infections? These interactions are poorly understood, as is the underlying pathophysiology and characteristics of different types of asthma throughout childhood into adulthood. The "atopic march" indicates that one clinical allergic disease presentation should be succeeded by the next; however, the denominator setting for this developmental cascade is not clear. Recent hypotheses focus on epithelial barrier dysfunction, which may increase the likelihood of immunological responses to environmental compounds passing through a leaky membrane. Whilst high allergen exposure amongst sensitised individuals is associated with more severe disease, the relationship between allergen exposure and development of sensitisation, asthma and lung function is much more complex.

KEYWORDS: Allergy, asthma, child, inflammation, lung function, severe

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Through the understanding of lung physiology in early life and its relationship with allergy the current knowledge on the causation of asthma could be refined. For decades asthma was predominantly considered an allergic disease. This concept was underpinned by a series of epidemiological studies that demonstrated atopic or allergic sensitisation as a high risk factor for asthma [1–3]. This association is particularly consistent in childhood, and childhood asthma is often considered as part of the "atopic" or "allergic march", suggesting the temporal pattern of progression from atopic dermatitis to allergic rhinitis and asthma [4, 5]. A biological explanation is provided by the notion of the common inflammatory background, which is generally considered to be eosinophilic inflammation. However, this concept has recently been challenged, *e.g.* there is considerable variability in the strength of the association between allergic sensitisation and asthma,

with the rate of wheeze being attributed to atopy ranging from 0% in Turkey to 94% in China [6]. In addition, most atopic subjects, *i.e.* those producing immunoglobulin (Ig)E antibodies towards common inhalant and food allergens, do not have asthma [7]. There is an emerging focus on the different asthma phenotypes throughout a patient's life with and without allergic sensitisation, eosinophilic or non-eosinophilic inflammation dominating the biopsy specimens [8, 9], heterogeneity in response to treatment [10, 11] and the lack of "atopic" genotypes to identify asthma presentation. Furthermore, asthma-like clinical symptoms and signs, often referred to as "wheezy" disorders in children, are common prior to signs or documentation of allergic disease or allergic inflammation.

The role of lung function development in relation to asthma is unclear. Does reduced lung function in early post-uterine life infer a (causal) risk for later asthma? Or is it simply a marker of an ongoing disease development? If so what is the association between reduced lung function and allergic sensitisation and allergen exposure? In addition, viral infections are common in childhood and are important triggers for symptoms in children with established asthma; however, their role in asthma development is not clear. This major field of research will be discussed in terms of interaction with allergy for asthma development.

Finally, the largest obstacle to overcome, with regards understanding the role of lung function development and allergy in asthma, is the lack of understanding what asthma is, not only do we need to define the various phenotypes involved but we must also comprehend their underlying immunopathology. One of the reasons for these inconsistencies, with respect to the association between atopy and asthma, may be the phenotypic heterogeneity. Thus, before reviewing the relationship between lung development, asthma and allergy it is important to discuss the meaning of the diagnostic labels used for atopy and asthma.

Definitions of asthma and allergy

Currently there is no consensus on the underlying pathophysiology for asthma throughout childhood and no universally accepted definition of the disease that is applicable to infants and 17-year-olds alike. One of the difficulties when studying asthma arises from it not being a single disease, rather a collection of diseases presenting as a syndrome or a collection of symptoms [12–16]. This is particularly relevant during childhood, when wheezing may be a final, common feature of several different diseases with distinct aetiologies and different genetic associates [13, 15]. In addition, childhood asthma often relies on parental reports of wheezing. This may be unreliable as parents could have little understanding of what physicians mean by the term "wheeze", either by contextual lack of the concept within the English language or more problematically in languages where wheeze is not a recognised word [17].

For the majority, asthma starts in early childhood [18], and the severity and number of wheezing episodes is a reasonable predictor for later childhood asthma [19, 20]. In addition, early childhood asthma, particularly in boys, is a significant risk factor for the development of chronic obstructive pulmonary disease (COPD) in adulthood [21]. Thus identifying "true" asthma in early childhood is challenging and requires an understanding of various subtypes of "asthma" presentations.

Different approaches in the identification of "phenotypes" for childhood and adult asthma have been used. One approach is to try and reach consensus based on published evidence. A consensus statement by the European Respiratory Society (ERS) Task Force on Preschool Wheeze defined phenotypes of preschool wheezing disorders based mainly on the predominant trigger, and proposed the terms "episodic viral wheeze" to describe children who wheeze intermittently and who are well between episodes, and "multiple-trigger wheeze" for those who wheeze both during and outside discrete episodes (acknowledging a large overlap between the two phenotypes, and the fact that individual patients may move from one phenotype to another) [22]. In another consensus report, the categorisation of wheeze phenotypes was shifted towards describing when and how often symptoms occurred as a guide to management [23]. Relatively poor reliability of

such clinical classifications for preschool wheeze has been suggested by a recent study that demonstrated ''episodic viral wheeze'' and ''multiple-trigger wheeze'' to be unstable phenotypes over a 12-month period [24].

Another approach is to use data collected over a time series and to assign a phenotype based on temporal patterns of wheezing by using answers to a repeated question (usually: ''Has your child had wheezing or whistling in the chest in the last 12 months?''). A classic example of this approach was the phenotyping described in the Tucson Children's Respiratory Study (TCRS), which assigned children to transient early wheezing, late-onset wheezing, and persistent wheezing [25].

Several recent publications have demonstrated that unbiased, clustering approaches may be useful in the analysis of multidimensional data to identify different asthma phenotypes. For example, results of the latent class analysis on a large dataset collected annually over a 7-year period in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort identified six childhood wheezing phenotypes [13]. In the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study this was reproduced to a significant degree; although the latter cohort identified five *versus* six categories observed in the ALSPAC cohort [26]. A principle components analysis was used to answer multiple questions relating to wheeze in the Manchester Asthma and Allergy Study (MAAS), which identified five syndromes of coexisting symptoms that may reflect different underlying pathophysiological processes [15]. In adult asthma, unsupervised hierarchical cluster analysis identified five distinct clinical phenotypes in the US Severe Asthma Research Program [14]. A similar approach in Leicester, UK, identified two clusters specific to refractory asthma, which were characterised by discordance between symptom expression and eosinophilic airway inflammation [12]. All these studies emphasised the need for new approaches in the classification of asthma phenotypes. In the extension of the clusters of severe asthma in adults, identification of intermediate phenotypes have been proposed, such as eosinophils, bronchial hyperresponsiveness (BHR), bronchodilator response *etc.*, which are modelled by various statistical approaches to further define clusters of possible underlying mechanisms in various clinical presentations [27].

Similar considerations may be true in relation to atopy. Whilst in epidemiology and clinical practice we often define atopy as a positive allergen-specific serum IgE (*e.g.* an IgE level >0.35 kUa·L^{-1}) or a positive skin-prick test (usually wheal diameter $\geqslant 3$ mm) to common food or inhalant allergens, these tests indicate only the presence of allergen-specific IgE. A considerable proportion of atopic individuals have no evidence of asthma or other allergic diseases [28]. Several studies have demonstrated that the level of specific IgE antibodies offers more information than the presence of specific IgE [29–31], and it is now recognised that amongst young wheezy children, allergen-specific IgE quantification may help identify those who are at risk for the later development of persistent asthma [31, 32]. It has recently been suggested that atopy may include several different phenotypes that differ in their association with asthma [33]. If this hypothesis is confirmed, then detectable serum IgE or positive skin-prick tests should be viewed as secondary or intermediate phenotypes of ''true'' allergic vulnerability, *i.e.* atopy should not be considered as a single phenotype but the sum of a number of atopic vulnerabilities [33]. Furthermore, the role of local tissue IgE production compared with serum detection of specific IgE antibodies is less well known [34–36], but may be involved in ''allergic reactions'' in which specific IgE antibodies are absent in the serum. These findings may explain some of the inconsistencies in the results of studies investigating the association between allergy, rhinitis and asthma [36].

In this chapter, rather than using uniform definitions of asthma and atopy, the role of lung development and allergy-associated mechanisms will be discussed in relation to age and varying presentation of childhood wheezing disorders, acknowledging the likelihood of differences in underlying pathophysiology. Thus, we accept that we do not know how many different ''asthmas'' or ''atopies'' there are during childhood, and what characteristics and pathophysiological mechanisms are involved in these different childhood asthma and atopy phenotypes.

Allergic inflammation

Allergic inflammation has commonly been regarded as a tendency towards the production of T-helper cell (Th) type 2, and their subsequent cascade of inflammatory mediators. The current concept of allergic inflammation is clearly more nuanced, with influences of regulatory T-cells playing a central role. In addition, the role of epithelial barrier deficiencies [37] is gaining increasing attention, suggesting that reduced epithelial barrier function may facilitate the uptake of proteins, such as allergens, with the subsequent immune responses being skewed towards the classical allergic diseases, such as asthma and atopic eczema [38]. This concept is supported by recent genetic evidence [39] and biopsy findings in human lung and skin tissue, as well as in animal models [37].

Detailed descriptions of the allergic inflammation and underlying immunological mechanisms are beyond the scope of the present chapter. However, a brief discussion will highlight the complexity of the physiopathology of allergic immune responses, which are influenced by genetic susceptibility, route of exposure, allergen dose and sometimes also the structural characteristics of the allergen [40–42]. Allergen exposure may lead to differentiation and clonal expansion of Th2 cells, and cytokines like interleukin (IL)-4 and IL-13 induce immunoglobulin class switching to IgE and expansion of naïve B-cell populations, and further clonal expansion in IgE-expressing memory B-cells [43]. Upon crosslinking of the IgE–FceRI (high affinity IgE receptor) complexes by allergen, basophils and mast cells degranulate, releasing vasoactive amines (mostly histamine), lipid mediators (prostaglandins, eoxins and cysteinyl leukotrienes), cytokines and chemokines, all characteristic of the immediate phase of the allergic reaction. Histamine, a key factor of the immediate phase of the allergic reaction regulates dendritic cells, T-cells and antibody isotypes *via* distinct histamine receptors. Both naturally occurring CD4+ and CD25+ regulatory T (Treg) cells, and inducible populations of allergen-specific IL-10-secreting Treg type 1 cells contribute to the control of allergen-specific immune responses [44].

Allergic diseases, clinical presentation and comorbidities

The allergic diseases often present in a pattern commonly referred to as the ''atopic (or allergic) march'' [5, 38, 45–49] and include asthma, atopic eczema, food allergy, allergic rhinitis, urticaria and anaphylaxis. IgE-mediated mechanisms are often, but not always, involved and the diseases appear to coexist more often than they present singularly. Being IgE sensitised to an allergen increases the risk of later allergic diseases, exemplified by a study undertaken in Australia that prospectively studied children with allergic sensitisation aged 18 months, but without asthma, allergic rhinitis or atopic eczema [50]. At 5-years of age the relative risk of asthma and rhinitis were 4.7 and 1.8, respectively, suggesting a progression from IgE sensitisation to allergic disease manifestation [50].

The label of atopic march indicates that one clinical presentation should be succeeded by the next manifestation, based upon the observation of incidence figures; atopic eczema and food allergens being most common in the first 2 years of life, asthma starting in the first year of life, but increasing in incidents in the next few years, followed by the development of inhalant allergies and eventually allergic rhinitis, presenting more commonly towards and in school-aged children. Additionally urticaria and anaphylaxis may occur at any time during childhood and adulthood, and any of these allergic presentations may occur for the first time at any point during life, either as a single entity or as part of a multiple-allergic disease manifestation. The heterogeneity of asthma, alluded to in 1981 by AAS [51], is likely to be true for each of the allergic diseases, with frequent allergic disease comorbidities in childhood. The asthma- and allergy-focused birth cohorts across the world are currently providing insight into how common and with what frequency these manifestations occur. In the Environment and Childhood Asthma (ECA) birth cohort study in Norway, 87% of the 10-year-old children with chronic rhinitis had at least one allergic comorbidity and 43% had a minimum of two [52]. Asthma, atopic eczema and

conjunctivitis coexisted in 11.8% of the children with rhinitis, whereas 3% of the entire study population had all four clinical presentations [52], somewhat higher than the 0.6–1.1% reported in 13 to 14-year-old children recounted in the phase III of The International Study of Asthma and Allergies in Childhood (ISAAC) study [53]. The presentation of current comorbidities is likely to vary with age, reflecting the undulating character of most allergic diseases. In addition, the role of psychosocial factors should not be underestimated [54, 55].

A possible link between a reduced barrier function and the development of allergic diseases may, to some extent, propose a possible mechanism related to the progression from one atopic manifestation to the next [38, 56, 57]. Filaggrin (FLG) mutations, combined with eczema in the first year of life, were associated with the later development of asthma and hayfever in the Dutch PIAMA cohort, whereas carriage of one or more FLG null-alleles was more common in inflammatory bowel disease (IBD) patients with atopy when compared to those without atopy (52% *versus* 14%, respectively) [58]. The effect of FLG null-alleles was strongest for eczema and food allergy and the presence of more than one atopic disease tended to increase the associated risk by up to 12.2-fold for the coexistence of eczema + asthma + allergic rhinitis + food allergy. Thus, the observed increased comorbidity of IBD with atopy was not explained by a common barrier genetic polymorphism, although FLG null-alleles contributed to coexistent eczema and food allergy [59].

Although sex differences in allergic diseases are well recognised, few studies have assessed whether or not the atopic march is relevant in boys as well as in girls. The changing male asthma preponderance in early childhood shifting to a female preponderance in adulthood [60], may suggest a sex difference in gene–environment and allergy interactions, illustrated by a lack of predictability of specific IgE antibodies at 2 years of age for asthma 6 years later in girls, but not in boys [31]. This issue should receive further attention in order to better understand the sex shift of allergic diseases through puberty.

Allergens and asthma severity

Several cross-sectional studies have reported the association of markers for asthma severity with the presence of allergen sensitisation and high exposure to sensitising allergens [61–66], emphasising the importance of allergy in diminished lung function and asthma severity. For example, the airway hyperreactivity, peak expiratory flow rate (PEFR) variability and lung function in dust mite-sensitised asthmatics correlate with mite-allergen exposure [61]; sensitisation and high exposure to sensitising allergens more often occurs amongst patients with severe brittle asthma than in those with mild disease [65]; and amongst atopic asthmatics, exhaled nitric oxide and other markers for asthma severity were higher in those who had been exposed to allergens causing sensitisation when compared with those that had not been exposed [62–64, 67].

Alternatively, numerous studies have reported a strong association of asthma exacerbations in childhood and adulthood with viral infections [68–71], and have proposed mechanisms that involve virus-induced exacerbations [68]. These data have been interpreted as proof that a viral infection (and not an allergy) is a major determinant for asthma exacerbations. Furthermore, it has recently been proposed that persistent respiratory infections may play a central role in the development of ''intrinsic'' asthma [72]. However, in reality patients are often exposed to viruses and allergens contemporaneously, therefore, it is possible that rather than being mutually exclusive viruses and allergies may interact to increase the risk of an asthma exacerbation [73]. For example, in studies investigating modifiable risk factors for asthma exacerbations, a synergism has been shown between allergen sensitisation and high domestic exposure to sensitising allergens with respect to respiratory viral infections (predominantly rhinovirus), and an increase in the risk of asthma exacerbations resulting in hospital admission amongst both adults [74] and children [75]. Interestingly, in the paediatric study, the level of IgE antibodies was a strong predictor for an increased risk of hospital admission due to acute asthma, and quantification of sensitive IgE antibodies gave more accurate prediction of hospitalisation than the presence of a positive allergy test [76].

The interplay between allergy and infection has also been suggested in disease pathogenesis; a recent study reported an association between bacterial-specific IgE and asthma susceptibility amongst teenagers, suggesting a role for bacterial-specific Type-2 immunity [77]. Alternatively, in a Nordic collaborative study of severe asthma in schoolchildren [78, 79], the presence of allergic sensitisation and lung function values were poor predictors of asthma severity [78], whereas reduced quality of life and poly-sensitisation more accurately characterised the severe asthmatic children from the well-controlled children or those without asthma.

Avoiding allergic triggers in the treatment of asthma

Allergen avoidance is an important part of the treatment used for patients with an allergy (*e.g.* in food allergy, avoidance of offending foods is the most important aspect of the overall management strategy). This, coupled with the finding that high exposure to different allergens can trigger asthma attacks in sensitised individuals, was used as a foundation for the proposal that allergen avoidance should lead to an improvement in asthma control. Clearly, such intervention is a cornerstone of the management of occupational asthma; in this context, identification and complete avoidance of the causal allergen is often associated with a dramatic improvement in symptoms and lung function. However, a meta-analysis of studies, which investigated the effect of mite-allergen avoidance in the treatment of asthma, reported no effect of the interventions and concluded that current methods of mite-allergen avoidance should not be recommended [80]. The fact that there is little evidence to support the use of physical or chemical methods to control dust mite or pet allergen levels in the treatment of asthma [81] has often been used as an argument against asthma being an allergic disease and allergic mechanisms playing a pivotal role in asthma severity. However, whilst it is clear that the use of mattress encasings as a single intervention in adults with asthma and a mite allergy is mostly ineffective [82], this does not mean that effective allergen avoidance is an ineffective management strategy and that it should not be considered in the treatment of carefully selected allergic asthmatics. It is becoming increasingly clear that simple, single interventions lead to some reduction in mite [83, 84] and pet allergen [85, 86] levels in the dust reservoirs, but their effect on personal inhaled allergen exposure is minimal [87–89], and that only a comprehensive approach to environmental control can achieve [90] and maintain very low allergen levels [91].The US Inner-City Asthma Study adopted a wide-ranging individualised intervention and demonstrated a clear significant beneficial effect in children with asthma, with environmental control resulting in significantly reduced number of days with asthma symptoms, which was apparent within 2 months and was sustained over the 2-year study period [92]. The guiding principles of allergen avoidance in the management of asthma are to achieve a major reduction in exposure, commence the intervention early in the natural history, carefully identify patients who are likely to benefit from the intervention and tailor the intervention using the information on a patient's sensitisation and exposure status [84].

Allergens and the development of sensitisation and asthma

Whilst high allergen exposure amongst sensitised individuals is associated with more severe disease (see previous section), the relationship between allergen exposure and development of sensitisation, asthma and lung function is much more complex. It has been suggested that *in utero* exposure to inhalant allergens may prime the T-cell system before birth [93, 94]. However, mite-allergen specific cord blood mononuclear cell immunoproliferative responses are mite-exposure independent, whilst peripheral blood mononuclear cell immunoproliferative responses at the age of 1 year appear to be related to environmental mite exposure during infancy [95], supporting the concept of sensitisation to inhalant allergens occurring in early life, but not *in utero*. Several studies from the US reported an increased risk of sensitisation to cockroaches amongst children with increasing cockroach-allergen exposure [96–99]; similarly, high exposure to mouse allergen was associated with increased frequency of sensitisation to mice [100, 101]. Cross-sectional studies in older children [102] and adults [103] reported an

increase in risk of specific allergen sensitisation with increasing contemporaneous domestic exposure for dust mite and cockroach, but not cat allergen [104]. Several longitudinal studies investigated the role of domestic allergen exposure in the development of sensitisation. Some have demonstrated a linear dose–response relationship between dust mite and cat allergen exposure in early life and subsequent development of specific sensitisations [105, 106], although others have not confirmed this finding [107]. A protective effect of high cat-allergen exposure on cat sensitisation was observed in some studies [104, 108], suggesting that the dose–response relationship between allergen exposure and specific sensitisation may differ between different allergens (*e.g.* linear for dust mite and cockroach, bell-shaped for cat). Only one longitudinal study reported a significant relationship between early-life dust mite-allergen exposure and an increased risk of asthma at 11 years of age [109], but this association was observed in a small group of 69 high-risk children. Most other studies were not able to replicate these results and found no association between allergen exposure and asthma development [106, 107, 110, 111].

Avoiding allergens in the prevention of sensitisation and asthma

The question as to whether reducing allergen exposure in early life can reduce the risk of developing sensitisation and asthma is being addressed by several primary prevention studies [90, 104, 112–117]. Clinical outcomes, reported to date, appear inconsistent and often confusing, *e.g.* whilst the Isle of Wight study showed mite sensitisation and asthma were significantly reduced at the age of 8 years [118], the MAAS (UK) study [119] reported an increase in mite sensitisation [112]. Much longer follow-up is required before we can draw definitive conclusions and give any meaningful advice within the public health context.

On balance, the overall evidence from observational and intervention suggests that the relationship between allergen exposure and the development of sensitisation and asthma is likely to be determined by the type of allergen, timing, pattern, dose and type of exposure, as well as other interacting factors.

Asthma, lung function and the role of allergy

Lung function development through childhood

By 24 weeks gestational age the airways have subdivided into approximately 17 generations, with a further seven orders of airway development forming during post-natal life, and the terminal sacs are present making gas exchange possible. Primordial alveoli are present from approximately 32 weeks, but characteristic mature alveoli develop mainly after birth [120], sometime during early childhood [121]. Lung volume increases are mainly due to an increasing number of alveoli up to about 3 years of age, but may still develop up to the age of 8 years [120]. In contrast, the number of conducting airways is complete at birth and an increase in size occurs thereafter [122]. After alveolar multiplication is complete, lung growth is assumed to be isotropic, with symmetrical development of lung size and airway size [122]. This suggests potential insults may affect lung development differently depending on the time of exposure.

Measuring lung function during different time-points through childhood has demonstrated substantial tracking of lung function, meaning that future lung function values are predicted by early measurements. This tracking maybe almost as great as tracking in height (tracking index $\tau > 0.90$) when evaluating forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) [123]. Only a small number of birth cohort studies have evaluated lung function longitudinally [124–127], and even fewer have measured lung function from birth [128, 129]. The effect of *in utero* exposures may be observed at birth, and may persist throughout childhood, as is the case for the reduced lung function found around birth in offspring of females who smoked during pregnancy [130–132].

Lung function in preschool age: relationship with allergy, persistence and the new onset of wheezing

Lung function is clearly an important determinant of asthma and wheezing, with a strong element of tracking. Tracking from infancy was not confirmed in 11-year-old non-wheezing children in Perth (Australia) comparing partially forced expiratory flow (FEF) volume curves (obtained by the rapid thoracic compression technique) to regular FEF volume loops, whereas children with persistent wheeze at the age of 11 years had reduced lung function shortly after birth as well as at 6 and 11 years of age [133]. Findings from the Tucson study demonstrated that a reduced lung function in children with persistent wheeze was only found at the age of 6 years, whilst transient early wheezers were observed as having a reduced lung function at both 6-years of age and shortly after birth [134], and those with the lowest lung function at birth remained so at the 22-year follow-up [124]. Likewise, in the ECA study in Oslo (Norway), lung function was significantly reduced at 2 years in children with recurrent bronchial obstruction, but this relationship was already present at birth. Thus, although reduced lung function appears to precede asthma development [128, 135, 136], other factors related to asthma also appear to have independent effects on lung function. Lower respiratory tract infections (LRTIs) have been associated with reduced FEF values, but not lung volumes in school-aged children [137–140]. However, the ECA study in Oslo recently suggested that the association was spurious, rather than causal. The observed reduced lung function in the 10-year-old children with the most LRTIs in the first 2 years of life was already present at birth and may be a marker of an increased susceptibility to LRTIs among children who are also at risk of asthma [141].

The interaction between lung function and asthma (phenotype) development is not clear. Several studies have shown reduced lung function prior to [25, 128, 136, 142–144] or at the time [136, 145, 146] of an obstructive airway disease in early childhood. However, identifying different temporal wheeze or asthma patterns by lung function reductions is more challenging. In the MAAS (UK) study it was found that among children with a history of wheezing within the first 3 years of life, lung function was reduced in those who subsequently continued with wheezing (persistent wheezers) compared with children who stopped wheezing after the age of 3 years (transient early wheezers); *i.e.* reduced lung function at the age of 3 years predicted the subsequent persistence of symptoms in children who had wheezed within the first 3 years of life [147]. However, when lung function was assessed at 3 years of age among children who had not wheezed by that time-point, no difference was found between those children who had not wheezed after this time-point compared with those who developed wheeze after the age of 3 years (late-onset wheezers); *i.e.* there was no association between lung function at 3 years of age with the new onset of wheeze after the age of 3 years, amongst children who had not wheezed in early life [147]. Similarly, in the ECA study, lung function was significantly reduced in children at the age of 2 years who had recurrent wheeze as well as atopic eczema [129]; however, the pattern was in fact already present at birth.

We have also shown that amongst children with a history of wheezing that within the first 3 years of life a reduced lung function and atopic sensitisation at 3 years of age predicts the subsequent persistence of wheezing [147], suggesting that both a primary lung determinant (reflected by the impaired lung function in early life) and a systemic immune response (observable as IgE-mediated sensitisation) underlie the development of persistent wheezing during childhood.

It is of note that even in the absence of respiratory symptoms, atopic children have impaired lung function compared with those who are not atopic as early as the age of 3 years [148]. In addition, the combination of allergen-specific sensitisation and a high level of exposure to sensitising allergen are associated with significantly poorer lung function amongst preschool children aged 3 years of age [148]. This observation has recently been extended by the finding that sensitisation to indoor allergens, which developed in the first 3 years of life was associated with a subsequent loss of lung function at school age, with concomitant high exposure to sensitising allergens aggravating this process [125]. In this study, the key features of asthma (airway hyperresponsiveness and

impairments of lung function) at school age were determined by early-life allergen sensitisation and high allergen exposure during the first 3 years of life [125]. Turning the question the other way round; are asthma phenotypes associated with reduced lung function? Clearly, the answer for many of the phenotypes is yes, as has been shown in many prospective birth cohorts (see previously) as well in the temporal wheeze phenotypes demonstrating remarkably similar associations to lung function in the ALSPAC and PIAMA studies [26]. However, the question still remains: how much of the reduced lung function was present at birth? And how much lung function deficit is attributable to other factors, such as environmental exposures?

The association between lung function and asthma appears to differ in childhood compared with adults. For example, airways remodelling, which is a key feature for reduced lung function in adult asthma, is not present in early childhood [149] and it is unclear whether it is has a major role in children with severe asthma [150, 151]. A recent study reported biopsy findings in 5- to 14-year-old children similar to those found in adults with severe persistent bronchial obstruction of an increased surface area of airway smooth muscle, as well as increased vascular network [152]. Also, the lungs and airways of children have a potential for growth and development [121], which is not the case in adults. Thus, an insult in early childhood may have a different and possibly a more favourable prognosis in children than in adults and should merit objective measures to be able to follow such development.

Genetics of early-life lung function

Studies of familial correlation and segregation of airway function suggest that genetic factors contribute to the regulation of airway growth [153]. The specific genes involved in these processes have not, as yet, been clearly identified. Several recent studies reported meta-analyses of genome-wide association studies for lung function, identifying a number of novel genome-wide significant loci [154, 155]. However, only a small minority of subjects were children and the discovered loci accounted for a very small proportion of the variation in lung function measures (<1%) [156]. Furthermore, all of the included analyses were based on cross-sectional measures of lung function [155]. In order to identify determinants of development and decline in lung function over time, it will be essential to carry out additional genetic studies in cohorts with longitudinal lung function data [155].

We have provided evidence of the association between polymorphisms in *ADAM33* and lung function in early childhood [157], suggesting that association between *ADAM33* and asthma may be mediated *via* its effects on lung function in early childhood. This indirectly supports the hypothesis that impaired early-life lung function is, in part, a genetically determined trait. We found no association between *ADAM33* single nucleotide polymorphisms (SNPs) and allergic sensitisation, suggesting that separate genetic factors contribute to disordered airway function and the immunological component of asthma [157]. In addition, there was a significant association between *ADAM33* polymorphisms and transient early wheeze, but not late-onset wheeze, supporting the idea that childhood asthma is a heterogeneous disease and that different genetic and environmental factors may be important in the different wheezing phenotypes.

Conclusions

So, what is the relationship between lung development, asthma and allergy? The evidence is mounting that neither ''asthma'' nor ''allergy'' are single phenotypes, but are a sum of a number of different conditions. The complex coexistence of the ''allergic diseases'' and the notion that allergy may be a systemic rather than an organ-specific disease provides a rationale for focusing research on untangling disease-specific and intermediate phenotypes. Lung function is clearly involved in asthma development, but it is still unclear whether reduced lung function at birth is a marker for later asthma, and to what extent allergy, environmental exposure to allergens and other factors may further reduce lung function during childhood.

With an increased understanding of the underlying respiratory physiology, serial lung function measurements in young preschool children may enable targeting of those who are most likely to benefit from treatment interventions and monitoring, as well as an improved understanding of the link between reduced lung function and the development of asthma and other allergic manifestations.

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K.C. Lødrup Carlsen is part of the MeDALL project.

Statement of Interest

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References

1. Simpson BM, Custovic A, Simpson A, *et al.* NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin Exp Allergy* 2001; 31: 391–399.
2. Addo-Yobo EO, Custovic A, Taggart SC, *et al.* Risk factors for asthma in urban Ghana. *J Allergy Clin Immunol* 2001; 108: 363–368.
3. Al-Mousawi MS, Lovel H, Behbehani N, *et al.* Asthma and sensitization in a community with low indoor allergen levels and low pet-keeping frequency. *J Allergy Clin Immunol* 2004; 114: 1389–1394.
4. Illi S, von Mutius E, Lau S, *et al.* The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113: 925–931.
5. Ker J, Hartert TV. The atopic march: what's the evidence? *Ann Allergy Asthma Immunol* 2009; 103: 282–289.
6. Weinmayr G, Weiland SK, Björkstén B, *et al.* Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Care Med* 2007; 176: 565–574.
7. Custovic A, Arifhodzic N, Robinson A, *et al.* Exercise testing revisited. The response to exercise in normal and atopic children. *Chest* 1994; 105: 1127–1132.
8. Saglani S, Bush A. Asthma, atopy, and airway inflammation: what does it mean in practice? *Am J Respir Crit Care Med* 2008; 178: 437–438.
9. Saglani S, Bush A. The early-life origins of asthma. *Curr Opin Allergy Clin Immunol* 2007; 7: 83–90.
10. Szefler SJ, Martin RJ, King TS, *et al.* Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002; 109: 410–418.
11. Szefler SJ, Phillips BR, Martinez FD, *et al.* Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005; 115: 233–242.
12. Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178: 218–224.
13. Henderson J, Granell R, Heron J, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63: 974–980.
14. Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181: 315–323.
15. Smith JA, Drake R, Simpson A, *et al.* Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008; 177: 1358–1363.
16. Lötvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
17. Lowe L, Murray CS, Martin L, *et al.* Reported *versus* confirmed wheeze and lung function in early life. *Arch Dis Child* 2004; 89: 540–543.
18. Burr ML, Merrett TG, Dunstan FD, *et al.* The development of allergy in high-risk children. *Clin Exp Allergy* 1997; 27: 1247–1253.
19. Castro-Rodríguez JA, Holberg CJ, Wright AL, *et al.* A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162: 1403–1406.
20. Devulapalli CS, Carlsen KC, Håland G, *et al.* Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008; 63: 8–13.
21. Svanes C, Sunyer J, Plana E, *et al.* Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010; 65: 14–20.
22. Brand PL, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096–1110.

23. Bacharier LB, Boner A, Carlsen KH, *et al.* Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63: 5–34.
24. Schultz A, Devadason SG, Savenije OE, *et al.* The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010; 99: 56–60.
25. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133–138.
26. Savenije OE, Granell R, Caudri D, *et al.* Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011; 127: 1505–1512.
27. Brasier AR, Victor S, Ju H, *et al.* Predicting intermediate phenotypes in asthma using bronchoalveolar lavage-derived cytokines. *Clin Transl Sci* 2010; 3: 147–157.
28. Nicolaou N, Poorafshar M, Murray C, *et al.* Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010; 125: 191–197.
29. Marinho S, Simpson A, Söderström L, *et al.* Quantification of atopy and the probability of rhinitis in preschool children: a population-based birth cohort study. *Allergy* 2007; 62: 1379–1386.
30. Simpson A, Söderstrom L, Ahlstedt S, *et al.* IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol* 2005; 116: 744–749.
31. Lødrup Carlsen KC, Söderström L, Mowinckel P, *et al.* Asthma prediction in school children; the value of combined IgE-antibodies and obstructive airways disease severity score. *Allergy* 2010; 65: 1134–1140.
32. Sly PD, Boner AL, Björksten B, *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; 372: 1100–1106.
33. Simpson A, Tan VY, Winn J, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010; 181: 1200–1206.
34. Hoddeson EK, Wise SK. The role of IgE production in the pathophysiology of rhinitis and rhinosinusitis. *Curr Allergy Asthma Rep* 2011; 11: 230–235.
35. Rondón C, Romero JJ, López S, *et al.* Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol* 2007; 119: 899–905.
36. Bertelsen RJ, Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. *Pediatr Allergy Immunol* 2010; 21: 612–622.
37. Holgate ST, Arshad HS, Roberts GC, *et al.* A new look at the pathogenesis of asthma. *Clin Sci (Lond)* 2010; 118: 439–450.
38. Zheng T, Yu J, Oh MH, *et al.* The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; 3: 67–73.
39. Holloway JW, Yang IA, Holgate ST. Genetics of allergic disease. *J Allergy Clin Immunol* 2010; 125: Suppl. 2, S81–S94.
40. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2011; 127: 18–27.
41. Akdis CA. T cells in health and disease. *J Allergy Clin Immunol* 2009; 123: 1022–1023.
42. Akdis M, Blaser K, Akdis CA. T regulatory cells in allergy. *Chem Immunol Allergy* 2006; 91: 159–173.
43. Akdis M, Akdis CA. Therapeutic manipulation of immune tolerance in allergic disease. *Nat Rev Drug Discov* 2009; 8: 645–660.
44. Larché M. Regulatory T cells in allergy and asthma. *Chest* 2007; 132: 1007–1014.
45. Food allergy, atopic dermatitis and the allergy march. Proceedings of a symposium in honour of Professor Luisa Businco. Venice, Italy, November 17–19, 2000. *Pediatr Allergy Immunol* 2001; 12: Suppl. 14, 5–107.
46. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112: Suppl. 6, S118–S127.
47. Hahn EL, Bacharier LB. The atopic march: the pattern of allergic disease development in childhood. *Immunol Allergy Clin North Am* 2005; 25: 231–246.
48. Lowe AJ, Carlin JB, Bennett CM, *et al.* Do boys do the atopic march while girls dawdle? *J Allergy Clin Immunol* 2008; 121: 1190–1195.
49. Luo J, Li Y, Gong R. The mechanism of atopic march may be the ''social'' event of cells and molecules (Review). *Int J Mol Med* 2010; 26: 779–785.
50. Almqvist C, Li Q, Britton WJ, *et al.* Early predictors for developing allergic disease and asthma: examining separate steps in the ''allergic march''. *Clin Exp Allergy* 2007; 37: 1296–1302.
51. Aas K. Heterogeneity of bronchial asthma. Sub-populations or different stages of the disease. *Allergy* 1981; 36: 3–14.
52. Bertelsen RJ, Lødrup Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. *Pediatr Allergy Immunol* 2010; 21; 612–622.
53. Ait-Khaled N, Pearce N, Anderson HR, *et al.* Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009; 64: 123–148.
54. Calam R, Gregg L, Simpson A, *et al.* Behavior problems antecede the development of wheeze in childhood: a birth cohort study. *Am J Respir Crit Care Med* 2005; 171: 323–327.
55. Calam R, Gregg L, Simpson B, *et al.* Childhood asthma, behavior problems, and family functioning. *J Allergy Clin Immunol* 2003; 112: 499–504.

56. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010; 105: 99–106.
57. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; 339: b2433.
58. Schuttelaar ML, Kerkhof M, Jonkman MF, *et al.* Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. *Allergy* 2009; 64: 1758–1765.
59. Van Limbergen J, Russell RK, Nimmo ER, *et al.* Filaggrin loss-of-function variants are associated with atopic comorbidity in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2009; 15: 1492–1498.
60. Vink NM, Postma DS, Schouten JP, *et al.* Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. *J Allergy Clin Immunol* 2010; 126: 498–504.
61. Custovic A, Taggart SC, Francis HC, *et al.* Exposure to house dust mite allergens and the clinical activity of asthma. *J Allergy Clin Immunol* 1996; 98: 64–72.
62. Langley SJ, Goldthorpe S, Craven M, *et al.* Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *J Allergy Clin Immunol* 2003; 112: 362–368.
63. Langley SJ, Goldthorpe S, Craven M, *et al.* Relationship between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitised, atopic asthmatic subjects. *Thorax* 2005; 60: 17–21.
64. Simpson AJ, Matusiewicz SP, Greening AP, *et al.* Pet ownership and asthma morbidity. *Respir Med* 2000; 94: 91–92.
65. Tunnicliffe WS, Fletcher TJ, Hammond K, *et al.* Sensitivity and exposure to indoor allergens in adults with differing asthma severity. *Eur Respir J* 1999; 13: 654–659.
66. Gore RB, Curbishley L, Truman N, *et al.* Intranasal air sampling in homes: relationships among reservoir allergen concentrations and asthma severity. *J Allergy Clin Immunol* 2006; 117: 649–655.
67. Langley SJ, Goldthorpe S, Custovic A, *et al.* Relationship among pulmonary function, bronchial reactivity, and exhaled nitric oxide in a large group of asthmatic patients. *Ann Allergy Asthma Immunol* 2003; 91: 398–404.
68. Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
69. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005; 24: Suppl. 11, S217–S22.
70. Johnston SL, Pattemore PK, Sanderson G, *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310: 1225–1229.
71. Johnston SL. Experimental models of rhinovirus-induced exacerbations of asthma: where to now? *Am J Respir Crit Care Med* 2003; 168: 1145–1146.
72. Dahlberg PE, Busse WW. Is intrinsic asthma synonymous with infection? *Clin Exp Allergy* 2009; 39: 1324–1329.
73. Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. *Proc Am Thorac Soc* 2004; 1: 99–104.
74. Green RM, Custovic A, Sanderson G, *et al.* Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002; 324: 763.
75. Murray CS, Poletti G, Kebadze T, *et al.* Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006; 61: 376–382.
76. Murray CSPG, Ahlstedt S, Soderstrom L, *et al.* Probability of hospital admission with acute asthma exacerbation increases with increasing specific IgE antibody levels. *Allergy Clin Immunol Int J World Allergy Org* 2007; 19: Suppl. 2, 270–273.
77. Hollams EM, Hales BJ, Bachert C, *et al.* Th2-associated immunity to bacteria in teenagers and susceptibility to asthma. *Eur Respir J* 2010; 36: 509–516.
78. Lang AM, Konradsen J, Carlsen KH, *et al.* Identifying problematic severe asthma in the individual child – does lung function matter? *Acta Paediatr* 2010; 99: 404–410.
79. Lang A, Mowinckel P, Sachs-Olsen C, *et al.* Asthma severity in childhood, untangling clinical phenotypes. *Pediatr Allergy Immunol* 2010; 21: 945–53.
80. Gøtzsche PC, Johansen HK, Schmidt LM, *et al.* House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2004; 4: CD001187.
81. Custovic A, Murray C, Simpson A. Allergy and infection: understanding their relationship. *Allergy* 2005; 60: Suppl. 79, 10–13.
82. Woodcock A, Forster L, Matthews E, *et al.* Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; 349: 225–236.
83. Fletcher AM, Pickering CA, Custovic A, *et al.* Reduction in humidity as a method of controlling mites and mite allergens: the use of mechanical ventilation in British domestic dwellings. *Clin Exp Allergy* 1996; 26: 1051–1056.
84. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). *Allergy* 2005; 60: 1112–1115.
85. Hodson T, Custovic A, Simpson A, *et al.* Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. *J Allergy Clin Immunol* 1999; 103: 581–585.
86. Green R, Simpson A, Custovic A, *et al.* The effect of air filtration on airborne dog allergen. *Allergy* 1999; 54: 484–488.

87. Gore C, Custovic A. Preventive measures and their effects. Results from cohort studies. *Paediatr Respir Rev* 2002; 3: 205–218.
88. Gore RB, Bishop S, Durrell B, *et al.* Air filtration units in homes with cats: can they reduce personal exposure to cat allergen? *Clin Exp Allergy* 2003; 33: 765–769.
89. Gore RB, Durrell B, Bishop S, *et al.* High-efficiency particulate arrest-filter vacuum cleaners increase personal cat allergen exposure in homes with cats. *J Allergy Clin Immunol* 2003; 111: 784–787.
90. Custovic A, Simpson BM, Simpson A, *et al.* Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000; 105: 252–258.
91. Simpson A, Custovic A. Early pet exposure: friend or foe? *Curr Opin Allergy Clin Immunol* 2003; 3: 7–14.
92. Morgan WJ, Crain EF, Gruchalla RS, *et al.* Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004; 351: 1068–1080.
93. Piccinni MP, Mecacci F, Sampognaro S, *et al.* Aeroallergen sensitization can occur during fetal life. *Int Arch Allergy Immunol* 1993; 102: 301–303.
94. Warner JO, Pohunek P, Marguet C, *et al.* Progression from allergic sensitization to asthma. *Pediatr Allergy Immunol* 2000; 11: Suppl. 13, 12–14.
95. Smillie FI, Elderfield AJ, Patel F, *et al.* Lymphoproliferative responses in cord blood and at one year: no evidence for the effect of *in utero* exposure to dust mite allergens. *Clin Exp Allergy* 2001; 31: 1194–1204.
96. Gruchalla RS, Pongracic J, Plaut M, *et al.* Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol* 2005; 115: 478–485.
97. Huss K, Adkinson NF Jr, Eggleston PA, *et al.* House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2001; 107: 48–54.
98. Rosenstreich DL, Eggleston P, Kattan M, *et al.* The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997; 336: 1356–1363.
99. Eggleston PA, Rosenstreich D, Lynn H, *et al.* Relationship of indoor allergen exposure to skin test sensitivity in inner-city children with asthma. *J Allergy Clin Immunol* 1998; 102: 563–570.
100. Phipatanakul W, Eggleston PA, Wright EC, *et al.* Mouse allergen. II. The relationship of mouse allergen exposure to mouse sensitization and asthma morbidity in inner-city children with asthma. *J Allergy Clin Immunol* 2000; 106: 1075–1080.
101. Custovic A, Bush RK. Two blind mice: new insights into mouse allergy. *J Allergy Clin Immunol* 2007; 120: 758–759.
102. Kuehr J, Frischer T, Meinert R, *et al.* Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994; 94: 44–52.
103. Custovic A, Simpson BM, Simpson A, *et al.* Current mite, cat, and dog allergen exposure, pet ownership, and sensitization to inhalant allergens in adults. *J Allergy Clin Immunol* 2003; 111: 402–407.
104. Custovic A, Hallam CL, Simpson BM, *et al.* Decreased prevalence of sensitization to cats with high exposure to cat allergen. *J Allergy Clin Immunol* 2001; 108: 537–539.
105. Wahn U, Lau S, Bergmann R, *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99: 763–769.
106. Lau S, Illi S, Sommerfeld C, *et al.* Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; 356: 1392–1397.
107. Cullinan P, MacNeill SJ, Harris JM, *et al.* Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004; 59: 855–861.
108. Platts-Mills T, Vaughan J, Squillace S, *et al.* Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; 357: 752–756.
109. Sporik R, Holgate ST, Platts-Mills TA, *et al.* Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990; 323: 502–507.
110. Burr ML, Limb ES, Maguire MJ, *et al.* Infant feeding, wheezing, and allergy: a prospective study. *Arch Dis Child* 1993; 68: 724–728.
111. Bertelsen RJ, Lødrup Carlsen KC, Carlsen KH, *et al.* Childhood asthma and early life exposure to indoor allergens, endotoxin and β(1,3)-glucans. *Clin Exp Allergy* 2010; 40: 307–316.
112. Woodcock A, Lowe LA, Murray CS, *et al.* Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; 170: 433–439.
113. Arshad SH. Indoor allergen exposure in the development of allergy and asthma. *Curr Allergy Asthma Rep* 2003; 3: 115–120.
114. Chan-Yeung M, Ferguson A, Watson W, *et al.* The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; 116: 49–55.
115. Koopman LP, van Strien RT, Kerkhof M, *et al.* Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002; 166: 307–313.
116. Marks GB, Mihrshahi S, Kemp AS, *et al.* Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006; 118: 53–61.
117. Simpson A, Custovic A. Prevention of allergic sensitization by environmental control. *Curr Allergy Asthma Rep* 2009; 9: 363–369.

118. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003; 58: 489–493.
119. Custovic A, Simpson BM, Murray CS, *et al.* The National Asthma Campaign Manchester Asthma and Allergy Study. *Pediatr Allergy Immunol* 2002; 13: Suppl. 15, 32–37.
120. Moore KL, Persaud TVN, Torchia MG. The Developing Human. Clinically Oriented Embryology. 8th Edn. Philadelphia, Saunders/Elsevier, 2008.
121. Galambos C, Demello DE. Regulation of alveologenesis: clinical implications of impaired growth. *Pathology* 2008; 40: 124–140.
122. Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. *Pediatr Pulmonol* 1996; 21: 383–397.
123. Dockery DW, Berkey CS, Ware JH, *et al.* Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. *Am Rev Respir Dis* 1983; 128: 405–412.
124. Stern DA, Morgan WJ, Wright AL, *et al.* Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; 370: 758–764.
125. Illi S, von Mutius E, Lau S, *et al.* Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; 368: 763–770.
126. Nicolaou NC, Simpson A, Lowe LA, *et al.* Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *J Allergy Clin Immunol* 2008; 122: 500–506.
127. Turner S, Zhang G, Young S, *et al.* Associations between postnatal weight gain., change in postnatal pulmonary function, formula feeding and early asthma. *Thorax* 2008; 63: 234–239.
128. Haland G, Lødrup Carlsen KC, Sandvik L, *et al.* Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006; 355: 1682–1689.
129. Haland G, Carlsen KH, Devulapalli CS, *et al.* Lung function development in the first 2 yr of life is independent of allergic diseases by 2 yr. *Pediatr Allergy Immunol* 2007; 18: 528–534.
130. Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, *et al. In utero* exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997; 10: 1774–1779.
131. Stick SM, Burton PR, Gurrin L, *et al.* Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996; 348: 1060–1064.
132. Hoo AF, Henschen M, Dezateux C, *et al.* Respiratory function among preterm infants whose mothers smoked during pregnancy. *Am J Respir Crit Care Med* 1998; 158: 700–705.
133. Turner SW, Palmer LJ, Rye PJ, *et al.* Infants with flow limitation at 4 weeks: outcome at 6 and 11 years. *Am J Respir Crit Care Med* 2002; 165: 1294–1298.
134. Morgan WJ, Stern DA, Sherrill DL, *et al.* Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005; 172: 1253–1258.
135. Martinez FD, Morgan WJ, Wright AL, *et al.* Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 1112–1117.
136. Young S, O'Keeffe PT, Arnott J, *et al.* Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis. *Arch Dis Child* 1995; 72: 16–24.
137. Mok JY, Simpson H. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. *Br Med J (Clin Res Ed)* 1982; 285: 333–337.
138. Woolcock AJ, Colman MH, Jones MW. Atopy and bronchial reactivity in Australian and Melanesian populations. *Clin Allergy* 1978; 8: 155–164.
139. Shaheen S, Barker DJ. Early lung growth and chronic airflow obstruction. *Thorax* 1994; 49: 533–536.
140. Castro-Rodríguez JA, Holberg CJ, Wright AL, *et al.* Association of radiologically ascertained pneumonia before age 3 yr with asthmalike symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999; 159: 1891–1897.
141. Håland G, Lødrup Carlsen KC, Mowinckel P, *et al.* Lung function at 10 years is not impaired by early childhood lower respiratory tract infections. *Pediatr Allergy Immunol* 2009; 20: 254–260.
142. Martinez FD, Morgan WJ, Wright AL, *et al.* Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. *Am Rev Respir Dis* 1991; 143: 312–316.
143. Yuksel B, Greenough A, Giffin F, *et al.* Tidal breathing parameters in the first week of life and subsequent cough and wheeze. *Thorax* 1996; 51: 815–818.
144. Murray CS, Pipis SD, McArdle EC, *et al.* Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population. *Thorax* 2002; 57: 388–392.
145. Lødrup Carlsen KC, Halvorsen R, Ahlstedt S, *et al.* Eosinophil cationic protein and tidal flow volume loops in children 0–2 years of age. *Eur Respir J* 1995; 8: 1148–1154.
146. Young S, Arnott J, O'Keeffe PT, *et al.* The association between early life lung function and wheezing during the first 2 yrs of life. *Eur Respir J* 2000; 15: 151–157.
147. Lowe LA, Simpson A, Woodcock A, *et al.* Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005; 171: 231–237.
148. Lowe LA, Woodcock A, Murray CS, *et al.* Lung function at age 3 years: effect of pet ownership and exposure to indoor allergens. *Arch Pediatr Adolesc Med* 2004; 158: 996–1001.

149. Saglani S, Malmstrom K, Pelkonen AS, *et al.* Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005; 171: 722–777.
150. Bush A. Update in pediatric lung disease 2007. *Am J Respir Crit Care Med* 2008; 177: 686–695.
151. Bush A. How early do airway inflammation and remodeling occur? *Allergol Int* 2008; 57: 11–19.
152. Tillie-Leblond I, de Blic J, Jaubert F, *et al.* Airway remodeling is correlated with obstruction in children with severe asthma. *Allergy* 2008; 63: 533–541.
153. Kurzius-Spencer M, Holberg CJ, Martinez FD, *et al.* Familial correlation and segregation analysis of forced expiratory volume in one second (FEV_1), with and without smoking adjustments, in a Tucson population. *Ann Hum Biol* 2001; 28: 222–234.
154. Hancock DB, Eijgelsheim M, Wilk JB, *et al.* Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 2010; 42: 45–52.
155. Repapi E, Sayers I, Wain LV, *et al.* Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2010; 42: 36–44.
156. Weiss ST. Lung function and airway diseases. *Nat Genet* 2010; 42: 14–16.
157. Simpson A, Maniatis N, Jury F, *et al.* Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-life lung function. *Am J Respir Crit Care Med* 2005; 172: 55–60.

Chapter 9

Genetics and epigenetics of childhood asthma

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SUMMARY: Asthma is a complex disorder caused by interaction of genetic and environmental factors.

In the last decade a lot of genes related to asthma and atopy were discovered. Candidate gene studies showed the involvement of genes related to innate and specific immunity, and replicated examples of interaction of genes and the environment. New genes identified through positional cloning studies, such as *ADAM33*, revived the interest in the airway epithelium and mesenchyme as important structural cells in asthma. Most genome-wide association studies discovered genes related to asthma that functions at the interface of airway structural cells and inflammation, such as *IL33*, *IL1RL1* and *TSLP*.

Epigenetics refers to heritable changes in gene expression without changes in DNA sequence, and includes DNA methylation, histone modifications and microRNAs. Several environmental factors known to be relevant in asthma may influence epigenetic modifications, however, the specific role of epigenetics in asthma is not clear. The ultimate goal of research in (epi)genetics of asthma is to identify susceptible subjects, and to contribute to (preventative) interventions.

KEYWORDS: Candidate gene association studies, DNA methylation, genome-wide associations studies, histone modification, microRNAs, positional cloning

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Asthma affects 300 million people throughout the world [1] and its prevalence is still increasing in the developing countries [2]. It is the most common chronic disease of childhood, with around 10% of the children in Western countries affected. Children are more often affected than adults (7–10% *versus* 3–5% in Western countries). As asthma is present in all ages and all ethnic backgrounds, the economic and societal burden to the worldwide community is large. For example, in 2003 the total costs of asthma in Europe were approximately €18 billion per year consisting of €10 billion in lost productivity and €8 billion in direct medical costs [3].

Asthma is a chronic inflammatory airway disease affecting the lower airways resulting in variable airflow obstruction and bronchial hyperresponsiveness (BHR). It causes recurrent episodes of coughing, wheezing, breathlessness and dyspnoea. In more severe and chronic asthma there is a degree of fixed airflow obstruction indicating the presence of airway remodelling.

Nowadays, asthma is not seen as a single disease but rather a collection of separate entities with variable expression and severity at different ages. Consequently, the variation in asthma phenotypes is wide, including allergic asthma, nonallergic asthma, exercise-induced asthma (EIA), and occupational asthma. In addition, the outcome of asthma at later age is also variable, where some children outgrow their asthma, in others asthma results in severe, persistent disease with irreversible airflow obstruction.

Risk factors for asthma can be divided into: 1) host factors such as sex, family history of asthma and atopy; 2) perinatal factors such as maternal smoking during pregnancy or mode of delivery; 3) environmental exposures in childhood such as the absence of breastfeeding, recurrent viral respiratory infections, environmental tobacco smoke exposure and air pollution and; 4) environmental exposures in adulthood, such as cigarette smoking, air pollution and occupational exposures. These risk factors may differ with age of onset of the disease, *e.g.* longitudinal studies have shown that sex and atopic status correlate with the age at the onset of asthma in children and adults.

The pathogenesis and, therefore, the causes of asthma are largely unknown. It is clear that next to inflammatory cells that compose the innate and adaptive immune system, airway structural cells (epithelial and mesenchymal cells) are important, as they may contribute to airway remodelling in asthma. Nowadays, it is thought that repeated injury of vulnerable airway epithelium by allergens or pollutants induces a cascade *via* the underlying mesenchyme which causes the airway inflammation and remodelling seen in asthmatic patients [4].

It is well recognised that asthma is a complex disorder in which a combination of genetic and environmental factors contribute. Recently, the potential contribution of epigenetic mechanisms in asthma has received much attention. The aim of this chapter is to provide an insight into what genetics and epigenetics have taught us so far in unravelling the mysteries of asthma. Specifically, we illustrate how increasing insights in genetics and epigenetics of asthma gives a better understanding of disease pathogenesis, as well as an increased understanding of how environmental factors interact with a subject's genetic makeup to develop disease. The ultimate goals of research in (epi)genetics of asthma are to identify susceptible subjects to enable early-life screening and contribute to (preventative) interventions and even prevent disease by environmental modification.

The heritability of asthma

Asthma runs in families. Twin studies and segregation analyses in different populations have shown that asthma has a strong genetic background and in most studies found a heritability of around 60% (range 32–78%). Heritability estimates the proportion of variance that is due to hereditary factors, which is not a fixed number, but dynamic and population specific as it depends on the environment.

Although asthma has a strong heritable component, the nature of this heritability (*i.e.* genetic or epigenetic) is not known. Genetic effects are caused by differences in DNA sequence, such as single nucleotide polymorphisms (SNPs), gene duplications or deletions, whereas epigenetic effects are heritable changes in gene expression that are not encoded in the DNA sequence itself. Epigenetic changes play a key role in activating or silencing genes, by DNA methylation, histone modifications and chromatin structure remodelling, as well as other gene regulatory networks, such as microRNAs (miRNAs) (table 1) [5–7].

In the past, different methods have been employed to identify genes for asthma, including candidate gene studies, positional cloning in families and, more recently, genome-wide association studies (GWAS). These approaches have generated numerous replicated genes associated with asthma. This part of the chapter describes the genetic research of asthma: how to identify asthma susceptibility genes using different genetic approaches, with a focus on genes which might be related to the development of childhood asthma. Where appropriate, gene–gene and gene–environment interaction in asthma will be addressed.

Table 1. Potential genetic and epigenetic effects in asthma

Genetic effects	Epigenetic effects
Chromosome deletions	DNA methylation
Common single nucleotide polymorphisms with modest effect	Histone modification
Rare variant with strong effects	Chromatin remodelling
Copy number variants	Small non-coding RNAs

Genetic research of asthma: how did we come this far?

Candidate gene approach

Candidate-gene association studies focus on genes that are thought to be involved in disease pathogenesis, based on their known biological function. Thus, it is a hypothesis dependent approach, in that the gene of interest is thought to be relevant to asthma. Preferably an SNP in the gene is selected that might possibly alter gene function. It investigates frequencies of alleles of a DNA polymorphism in the gene of interest between affected individuals and unaffected controls. Like all discovered genes, association of a risk allele in a candidate gene needs to be replicated in other populations to provide robust evidence for its role in asthma.

To date, over 1,000 genetic association studies in asthma and allergy have been performed. Figure 1 presents the findings of these studies published up to October 2011, summarising and updating earlier work of POSTMA *et al.* [8], OBER and HOFFJAN [9] and VERCELLI [10]. The figure reflects the number of positive reports of any DNA variation in candidate gene studies for any asthmatic or allergic phenotype. Of note, the unit of replication is the gene, and not a specific SNP, where the disease definition is broad, including asthma and allergic phenotypes (fig. 1). This has been termed "loose replication" [11], this strategy has been employed because: the alleles of different SNPs in a gene are often correlated within a population; different alleles of the same SNP may interact with the environment and both may be relevant in disease development; a gene may have multiple functional genetic variants; causative SNPs may differ between different ethnicities; and the phenotypes are highly correlated, especially in childhood. This strategy has been criticised for being too inclusive, and it has been argued that "strict replication" (*i.e.* same SNP, same allele and same phenotype definition) provides stronger evidence for the role of a certain SNP in disease development [10, 12].

The most strongly replicated candidate genes for asthma and allergy include genes that encode T-helper (Th)2 cytokines and their receptors, such as *IL4* and *IL13*, and their receptor *IL4RA*. These cytokines are important drivers of the Th2 response that is important in adaptive immunity, resulting in B-cell switching and immunoglobulin (Ig)E production. Notably, subjects carrying risk alleles in *IL4, IL13* and *IL4RA* genes have an increased risk of asthma, indicating gene–gene interaction [13, 14].

Furthermore, genes from innate immunity pathways that encode pattern recognition receptors, such as *CD14* that encodes the co-receptor for endotoxin, and *Toll-like receptor 4*, are also strongly replicated genes in allergy. The genes encode receptors that are at the interface of the host sensing the environment, and multiple gene–environment interactions have been reported. The best replicated gene–environment interaction is the association of *CD14* SNPs with allergy. This association appears to depend on the level of endotoxin exposure [15, 16].

A final example of a candidate gene approach was the discovery of *Filaggrin (FLG)* as a candidate gene for eczema, after its initial discovery as a gene involved in ichtyosis vulgaris. Two, loss of function variants are associated with a strong increase in risk of eczema [17, 18]. Interestingly, in those with *FLG* mutations and eczema, there is a high risk of asthma development. *FLG* is expressed by skin keratinocytes and involved in the epithelial barrier of the skin. These findings have led to the concept that the skin may be an important route for sensitisation to allergens, and that inflammation in the skin may have important consequences in the lung (fig. 2) [19, 20].

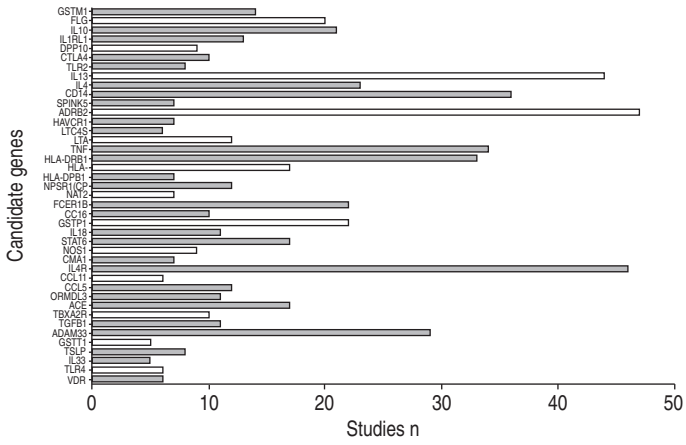

Figure 1. Summary of candidate gene studies in asthma reporting a positive association of a gene variant in asthma. The number of studies reporting a positive association of a gene variant in asthma is shown. The figure is based on the work of OBER and HOFFJAN [9], VERCELLI [10] and POSTMA *et al.* [8] who used a systematic literature search for genes associated with asthma and atopy phenotypes, asthma, bronchial hyperresponsivess, airway hyperresponsivess, atopy, skin prick test and immunoglobulin E. Literature search was extended to October 2011. For defining replication, the gene was the unit of replication, not the single nucleotide polymorphism. Reproduced from [8] with permission from the publisher.

Positional cloning

Positional cloning is the identification of a gene by genome-wide linkage analyses. It is a hypothesis independent approach and starts with the investigation of families in which the disease (asthma) is present in multiple family members. The genome of these families is screened with microsatellite markers (repeating sequences of two to six base pairs of DNA) evenly spaced throughout the entire genome and is tested for linkage with the disease phenotype. Linkage is found when a marker and a phenotype are inherited together more often than expected by chance. When linkage is found, further identification of the gene through scanning of SNPs in the linked region using case–control association analysis will help to define the critical region more accurately. Next, the genes found in this region can be examined for possible involvement in the disease process. This approach needs a lot of molecular genetic analysis which involves a lot of time and money [11, 21]. Moreover, it is very difficult to pin point one or more genes in a linked region of interest, due to the limited resolution of linkage and the presence of multiple disease-associated genes. For instance, the chromosome region 5q31-33 showed 14 genes involved in asthma, atopy or related intermediate phenotypes, such as *IL4, IL13, RAD50, CD14, PCDH1,* the *β_2-adrenergic receptor* and *serine peptidase inhibitor Kazal type 5 (SPINK5)*. Recently, BOUZIGON *et al.* [22] reported a meta-analysis of published linkage studies in asthma and associated phenotypes, and identified two genome-wide significant linkage peaks in European families ascertained through two siblings with asthma: chromosome 2p21-p14 and 6p21. Interestingly, atopic traits were significantly linked to 3p25.3-q24, 5q23-q33, and 17q12-q24 (skin prick tests), and chromosome 2q32-q34 (blood eosinophils).

In 2002, the first gene associated with asthma and BHR found through positional cloning was *a disintegrin and metalloprotease (ADAM)*33 located on chromosome 20p13 [23]. After the discovery of *ADAM33* gene several other genes related to asthma and/or allergy have been found through positional cloning: *dipeptidyl-peptidase 10* (*DDP10*) on chromosome 2q14, *major histocompatibility complex class I G on chromosome 6p21 (HLA-G), plant homeodomain finger protein 11(PHF11* on chromosome 13q14), *prostaglandin D2 receptor* on chromosome 14q21, *G protein-coupled receptor for asthma (GPRA)* on chromosome 7p14, *plasminogen activator, urokinase receptor (PLAUR)* on chromosome 19q13, *protocadherin 1 gene (PCDH1)* for BHR on chromosome 5q31-33, and *cytoplasmic fragile X mental retardation protein (FMRP)–interacting protein 2 gene* (*CYFIP2)* on chromosome 5q33 [10, 21, 24]. *IL-1 receptor-associated kinase-M* gene located on chromosome 12q13-24 is associated with early-onset persistent asthma. The biological function, as well as the role in asthma, still needs to be elucidated for many of these genes. However, it is remarkable that a lot of these new asthma genes are expressed in airway structural cells, potentially affecting the epithelial barrier and (re)modelling of the airways in asthma. Thus, positional cloning has renewed the interest of asthma researchers in the epithelium and smooth muscle. There are, however, several drawbacks of positional cloning studies, such as: 1) the limited power and

resolution of linkage resulting in difficulties in identification of the precise gene and genetic variant(s) underlying the observed linkage peaks; 2) the lack of reproducibility; and 3) risk of focusing on genes which have a positive signal and that have a biological plausibility for the development of the disease (''positional candidate gene approach'') instead of follwing up stronger signals. In this way, novel genes potentially implicating novel disease mechanisms may be missed.

Investigations of *ADAM33* illustrate the challenges of taking a novel gene forward, from extensive association studies to expression and functional studies. Progress has been made in characterising gene expression and function of gene transcripts, but functional genetic studies showing how asthma susceptibility SNPs alter gene function, thereby contributing to asthma, are still lacking. The association between multiple SNPs in *ADAM33* and asthma and BHR has been replicated in several case–control and family studies [25–27]. Despite confirming the association between asthma and BHR and the *ADAM33* gene, the actual associated SNPs have varied between studies [28] and, at present, the causative SNPs are not known. A few studies did not replicate the association between the *ADAM33* gene and asthma [29, 30]. These differences may be partially explained by the definition of asthma (*i.e.* including the presence of BHR) in these studies and differences in population and environmental factors. It is also suggested that *ADAM33* SNPs have only a moderate effect on the development of asthma, since the increased risk of developing asthma estimated from a meta-analysis of subjects carrying risk alleles was 1.4 [25]. Thus, large studies are needed to replicate this association. *ADAM33* was not only shown to be important in asthma susceptibility, but also severity, as SNPs in the *ADAM33* gene were found to be associated with accelerated decline in forced expiratory volume in 1 second (FEV_1) in asthma [31], and to decline in FEV_1 in the general population [32], but not to markers of atopy such as blood IgE levels or allergy skin-prick tests. In addition, SIMPSON *et al.* [15] showed that certain polymorphisms in the *ADAM33* gene predict impaired early life lung function. They investigated a prospective birth cohort and showed that certain SNPs were related to lower lung function at the age of 5 years. These associations suggest, but do not prove, that ADAM33 may be involved in airway growth, and in the ageing and remodelling processes in the lung.

No differences were found in ADAM33 expression between asthmatics and controls in lung biopsies [33, 34]. In contrast, soluble ADAM33 in bronchoalveolar fluid (BALF) is increased in asthmatics compared to controls [35]. FOLEY *et al.* [36] showed increased expression of ADAM33 in airway epithelium in patients with severe asthma, however, this remains controversial as these results could not be confirmed by several others [34, 37].

ADAM33 can have different functions due to the different functional domains present on this protein; these include activation of (matrixmetallo-) proteases, proteolysis, adhesion, fusion and intracellular signalling [38]. It is expressed in the airways in smooth muscle cells and lung fibroblasts, but not in inflammatory or immune cells [23, 37]. The soluble form of ADAM33 promotes angiogenesis [33], and its secretion is stimulated by transforming growth factor (TGF)-β_2, an important mediator of inflammation and remodelling, which is released upon epithelial damage. In asthma, ADAM33 is hypothesised to be important in lung embryogenesis and (re)modelling processes of the airways, *via* the epithelial mesenchymal tropic unit, *e.g.* the interaction between the epithelium and mesenchyme. Remodelling of the airway in asthma has long been assumed to result from uncontrolled inflammatory and repair processes, but evidence is accumulating that these processes may occur early in development, either as an effect of the maternally dictated (*in utero*) environment or genetically inherited factors, or a combination of both. ADAM33 may have a role in branching morphogenesis of the lungs, since it is present in embryonic lung tissue in the bronchi and surrounded mesenchyme. The expression of ADAM33 mRNA and protein is elevated during the early pseudoglandular stage and again *post-partum* and seems to influence the balance of growth factors at specific stages during lung development [34, 39]. It is suggested that certain polymorphisms of the *ADAM33* gene may influence the subsequent susceptibility of the lung to asthma [34, 38]. However, the finding that *ADAM33* knockout mice do not show changes in lung development or in an allergen-induced experimental asthma model has challenged the relevance of *ADAM33*, at least in this mouse model [40].

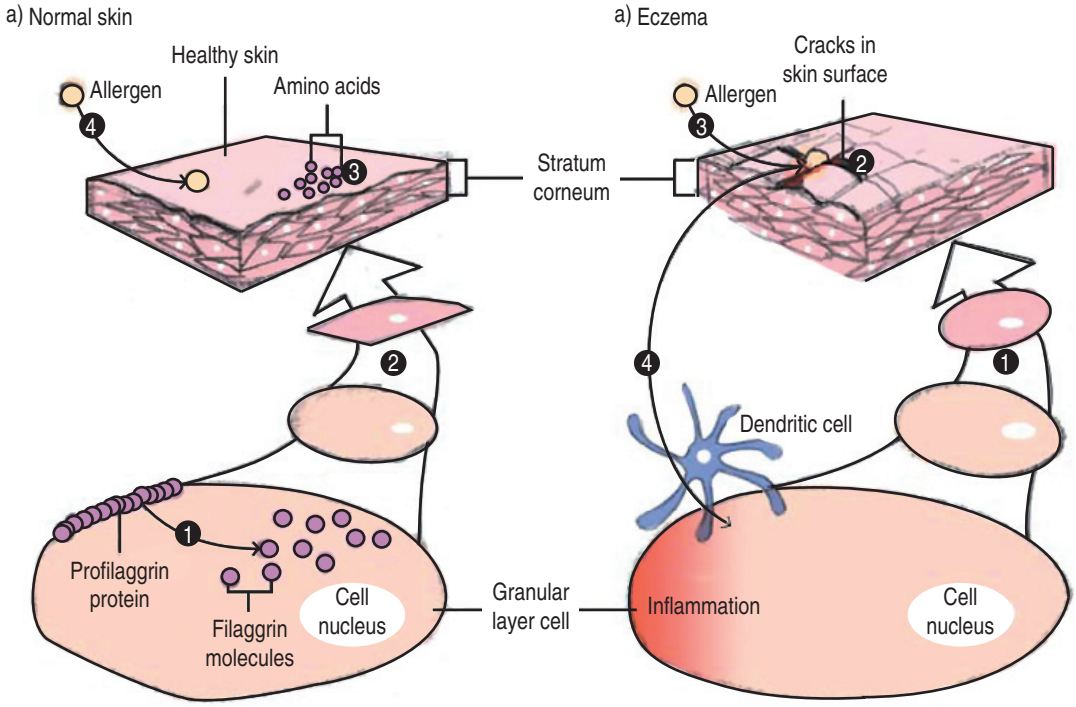

Figure 2. The role of filaggrin in the susceptibility of asthma. a) Normal skin. 1) In the granular layer of normal skin, the large profilaggrin protein is dephosphorylated and enzymatically cut into 10–12 smaller filaggrin molecules. 2) As these cells move up to form the stratum corneum, they flatten their shape by collapsing their keratin structure, a process aided by interaction with filaggrin proteins. 3) In the stratum corneum, filaggrin degrades into amino acids that are essential for maintaining moisture in the outer layers of skin. 4) The intact skin barrier of healthy skin keeps allergens, pathogens (bacteria and viruses) and chemical irritants out of the body. b) Eczema. 1) Mutations in the *filaggrin* gene greatly reduce the amount of filaggrin protein in the skin or lead to its complete absence. 2) This results in cracks in the skin barrier and 3) exposes the lower layers to allergens that are usually kept out, thus causing eczema. 4) Once foreign material, such as an allergen, passes through the defective skin barrier, it is identified by cells of the immune system, leading to inflammation of the skin and other allergic responses. If a child is exposed to allergens through the skin, the exposure is more likely to prime the immune system to react aggressively to that allergen later in life, explaining the coincidence of asthma and eczema observed in patients worldwide. Reproduced from [19] with permission from the publisher.

Genome-wide association studies

GWAS aim to find common genetic variants that may play a role in disease or identify the hereditable traits that are risk factors for the disease. The most important advantage of GWAS is the ability to discover novel disease genes as it does not depend on prior hypotheses, and consequently detects new mechanisms of the disease. Inclusion of large number of patients with the complete spectrum of disease severity will provide a complete picture of the disease and may, therefore, also detect genes related to more mild-to-moderate traits of the disease. It does not require the recruitment and phenotyping of large family-based samples like positional cloning. The use of GWAS became feasible after the development of genotyping chips which contain a dense set of hundreds of thousands of SNPs with good coverage of the human genome. In addition, the costs of these chips dropped sharply so it became easier for researchers to test DNA variants from large numbers of people. Since the GWAS design tests a large number of SNPs, a large number of subjects are needed to account for the multiple comparisons that are made. These large numbers of subjects can be derived from the general population or specific sets of families, which are then typically meta-analysed. The study design of a GWAS needs to incorporate

important aspects, such as a well-characterised study population with careful geographical matching of cases and controls, an extremely large sample size (with number of cases and controls in the thousands to tens of thousands of subjects), and adequate genotype quality to identify true positive signals. Furthermore, one has to realise that the identified SNP or set of SNPs may not be the SNPs themselves that are influencing the disease but only that they are located near the causative DNA variants. The identification of a gene or a region of interest using GWAS needs replication in different study populations and, just like candidate studies and positional cloned genes, needs further research addressing the function and role of the gene within the disease. It seems unlikely that GWAS are the sole solution to study complex diseases but is specifically helpful in the identification of common variants with relatively small effects.

In 2007, the first GWAS on asthma was published and reported the discovery of the association of DNA variants in the genes encoding the *orosomucoid 1 like 3* (*ORMDL3*) and *Gasdermin like* (*GSDML*), localised on chromosome 17q21, with childhood asthma [41]. These authors showed that *ORMDL3* gene variants are associated with mRNA expression of ORMDL3 in Epstein–Barr virus-transformed lymphoblastic cell lines of children with asthma. ORMDL3 mRNA was present in different types of tissues, including lymphocytes and lung tissue. *ORMDL3* is a member of a novel class of genes of unknown function and encode for transmembrane proteins anchored in the endoplasmatic reticulum; whereas *GSDML* is associated with epithelial integrity [42].

Subsequent GWAS on asthma have been conducted and discovered the following gene: *phosphodiesterase 4D (PDE4D)*, located on chromosome 5q12, was related to childhood asthma and is involved in airway smooth muscle contraction [43]. In addition, another member of the phosphodiesterase superfamily genes, *PDE11A* is associated with (allergic) asthma [44]. Another GWAS study in Mexican asthmatic children and their parents found association with an SNP in the gene *transducin-like enhancer of split 4* (*TLE4*) on chromosome 9q12.31, the exact role of this gene is not yet clear, however, it could be relevant in immune development (B-cell differentiation) [45]. *DENND1B* (encoding the *DENN/MADD domain containing 1B* protein) is expressed on dendritic cells and has also been associated with childhood-onset asthma [46]. In the TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes) study, multiple SNPs in the *RAD50-IL13* gene and the *HLA-DR/DQ* gene were associated with asthma which confirmed the important role of Th2 cytokine and antigen presentation genes in asthma [47]. In 2010, the EU GABRIEL consortium conducted a large GWAS study which included subjects from 23 studies (10,365 cases and 16,110 controls) and confirmed previous data regarding the association of the *ORMDL3/GSDML* locus, also called the 17q21 variants, with childhood-onset asthma, but also revealed the following genes associated with asthma: *IL1RL1/IL8R1* (chromosome 2), *HLA-DQ* (chromosome 6), *IL33* (chromosome 9), *SMAD3* (chromosome 15) and *IL2RB* (chromosome 22) [48].

Recently, a meta-analysis from GWAS of asthma in ethnically diverse US populations was published. This study replicated the 17q21 variants and SNPs near *IL1RL1, IL33* and *TSLP* and reported that these asthma loci were associated with different ethnic groups. Moreover, one novel locus near PYHIN1 was reported only in subjects of African descent [49]. The possibility that ethnic specific genetic effects on asthma may be present was further evidenced by a GWAS on asthma in the Japanese population. As well as confirming the *IL33* and *HLA* loci, three novel regions were reported: chromosome 4q31 (including *USP38* and *GAB1*), 10p14 and 12q13 [50].

Another method to investigate the possible genes related with asthma is *via* analysis of the genes related to measurable intermediate traits of asthma. An international consortium led by scientists for deCODE conducted a GWAS for sequence variants affecting blood eosinophil numbers and found an association between several SNPs associated with blood eosinophil counts, including SNPs in *IL33*, and *IL1RL1*. As a next step, these SNPs were shown to be associated with atopic asthma [51]. Another GWAS was conducted on chitinase-like protein YKL-40, which is known to be involved in inflammation and tissue remodelling and correlates with asthma severity. One promoter SNP in *CHI3L1*, the *chitinase 3-like 1* gene encoding YKL-40, was associated with elevated serum YKL-40 levels and subsequently shown to be associated with asthma and its related

phenotypes as well [52]. In summary, there are multiple replicated robust asthma loci emerging from GWAS that include 17q21 variants, *IL33, IL1RL1, TSLP, SMAD3* and multiple SNPs in the *HLA* region. It appears that most of these genes function at the interface of airway structural cells sensing environmental stimuli and the translation of these signals into an inflammatory response [53].

As an illustration, we will now discuss the investigation of the 17q21 signal in more detail. Since the discovery of the association of the "so called" 17q21 variants, including the *ORMDL3* and *GSDML* genes and childhood asthma in 2007, this association has been replicated in several other population studies which include European (French, Germans, British), North American, Mexican, Afro-American and Chinese people [50, 54–59]. In these studies the 17q21 SNPs were predominately related to childhood asthma, but not to adult asthma, which suggests a specific role for these genes in the development of childhood asthma. At the time of its discovery the association of these 17q21 variants with asthma was unknown. Since then further research has been performed investigating the functionality and the gene–environmental interaction of the so called "17q21 chromosome variants" and the (development) of asthma. BOUZIGNON *et al.* [59] showed that the association of 17q21 markers and early-onset asthma was increased when subjects were exposed to tobacco smoke early in life. They also reported that the disease-associated markers on chromosome 17q21 point to a relatively narrow region of interest that included four genes: *IKZF3* (involved in the regulation of lymphocyte development); *ZPBP2* or *zona pellucida-binding protein 2*; *GSDML*, encoding one of the gasdermin proteins implicated in epithelial barrier function and skin differentiation; and *ORMDL3* which encodes transmembrane proteins anchored in the endoplasmic reticulum. HIROTA *et al.* [56] showed that in a Japanese population *ORMDL3* was associated with childhood asthma, but was not related to IgE levels. Furthermore, they suggested a role for ORMDL3 in viral infection, since this was elevated in lung fibroblasts after stimulation with polyinosine-polycytidylic acid (which is an immunostimulant simulating viral infections). SMIT *et al.* [60] showed that having the 17q21 risk genotypes increased the positive association between early respiratory infection and asthma, and this was restricted to early-onset asthma and asthma that remits in young adulthood. The association between infection and early-onset asthma (or remittent asthma) was further enhanced when children with 17q21 risk variants were exposed to environmental tobacco smoke in early life. Whether respiratory infection is a marker identifying infants with a predisposition to develop asthma, or whether infection is causally related to the inception of asthma, remains to be elucidated. Furthermore, 17q21 polymorphisms were strongly associated with *ORMDL3* and *GSDMA* gene expression in cord blood stimulated with Der P1. In addition, 17q21 SNPs influenced interleukin (IL)-17 secretion in cord blood mononuclear cells pointing to a functional role of the 17q21 locus for T-cell regulation early in life [61]. These genes lay in a block of linkage disequilibrium, indicating that the risk alleles occur together in Western populations. This makes it difficult to untangle the specific functional role of a particular SNP. Functional studies have indicated that asthma associated SNPs in the 17q21 locus regulate the mRNA expression of three genes: *ORMDL3*, *GSDMB* and *ZPBP2* [57]. In a series of elegant experiments, VERLAAN *et al.* [62] were able to narrow down the region using cells lines from subjects of African descent, and showed that a novel SNP in this linkage disequilibrium block regulated nucleosome binding in an allele specific manner and thereby the transcription of *GSDML* and *ORMDL3*.

In conclusion, GWAS have provided new genes and new possible pathways in the development of asthma. Thus, suggesting that asthma with an onset early in life may differ biologically from asthma with a later onset.

Insights from genetic studies of asthma

Asthma genetics has provided an unbiased insight into asthma pathobiology. Although our understanding of gene function is still very limited, we can now start to formulate hypotheses on the implications of novel asthma genes found by positional cloning and GWAS for asthma pathobiology.

First, the integrity of the epithelium has been implicated by genes that encode adhesion molecules expressed in the epithelium (*GSDML* [41, 48], *CTNNA3* [63] and *PCDH1* [64]). The integrity of the airways is maintained by the formation of tight junction complexes [65], adequate repair responses upon injury in combination with terminal differentiation of airway epithelial cells, and processes that may be impaired in asthma [65, 66]. For example, *RORA* [48] is expressed in a gene cluster in keratinocytes implicated in epithelial cell differentiation [67], whereas the expression of PCDH1 is associated with the level of airway epithelial cell differentiation [68].

Secondly, mediators of epithelial stress or damage can provide alarm signals to activate Th2 inflammatory responses from the innate immune system (*IL-13*, *IL-33* and its receptor *IL1RL1*, and *TSLP*), and/or induce repair responses (*PLAUR* [69], *SMAD3* [48] and *CHI3L1* [52]). These repair responses may lead to activation of the mesenchyme and to smooth muscle contractility (*PDE4D*) and vascular remodelling (*ADAM33*).

Finally, immune system activation may include a variety of cellular mechanisms, including induction and activation of B- and T-cells (*PHF11* encodes a transcription factor observed in B- and T-cells, and *TLE4* is possibly involved in B-cell differentiation) and dendritic cells (*DENN1B*).

Future perspectives in the genetics of asthma

A lot of genes related to asthma have been discovered, revealing several pathways important in the development and pathogenesis of asthma, *e.g.* genes related to Th2-cell differentiation, and epithelial–mesenchymal interaction. In future, the use of GWAS, and even larger meta-analyses of GWAS, will possibly reveal more genes related to the development of asthma and can be used to investigate gene–environment and gene–gene interactions, which will be one of the next steps to be elucidated. Novel technology in DNA and RNA sequencing will provide an opportunity to investigate the role of novel DNA and RNA variants in asthma. Furthermore, genetic research needs to be directed towards functional studies of the so-called asthma genes, in order to define their exact role in the pathogenesis of asthma, how they interact with the environment, and how these pathways can be intervened upon in model systems [70]. One example of functional genetic studies is the integration of genomic methods by the systematic investigation of the role of SNPs on gene expression, known as eQTL (expression quantitative trait locus) mapping [71]. Evidence from other complex diseases suggests that approximately half of all susceptibility genes may harbour eQTLs that are linked to disease development [72].

What can we learn from genetic research for everyday life in the clinic? Genetic research can help to understand the pathogenesis of asthma. Understanding of the genetic basis of asthma will improve diagnosis and treatment in the future. It may help us to predict disease onset, to define different subsets of asthmatic patients (taking the gene–environment interactions into account) and predict severity of the disease. This knowledge can contribute to personalised treatment of patients and, research focussing on the development of asthma may even eventually lead to the prevention of the disease.

Epigenetics of asthma

What is epigenetics?

Epigenetics means broadly ''on top of genetics''. Currently, epigenetics is defined as heritable changes in gene expression that occur without direct alteration of the DNA sequence [73, 74]. In molecular terms it normally refers to important modifications in the processes of gene transcription and translation ultimately determining whether a gene is expressed or not. Epigenetic modifications account for the possibility of cellular differentiation, where patterns of gene expression allow for considerable cellular diversity, while the DNA code within the

differentiating cells remain unchanged. The past decades have brought on substantial progress in the understanding of epigenetic mechanisms. This has given us novel insight into how epigenetic modifications may affect disease susceptibility, but also how environmental exposures may affect epigenetic patterns [75]. Furthermore, although epigenetic states are extensively re-programmed between generations (associated with the pluripotent state that exists in early development), there are now a few studies demonstrating that certain epigenetic states (assessed by DNA methylation [76] or microRNA [77]) may occasionally be transgenerationally transmitted. Thus, where disease susceptibility was traditionally believed to be determined by inheritable information carried out on the primary DNA sequence, it is now becoming increasingly clear that regulation of gene expression, alongside genetic variation, are integral parts of the impact of genetics on disease.

However, the dynamic nature of the cell epigenome results in concrete challenges when it comes to performing, analysing and interpreting epigenetic data. First, up to now, most epigenetic studies have been performed with limited genome coverage or inadequate sample size [78]. As different whole genome scale epigenomic profiling technologies are presently becoming feasible, such concerns may be addressed in future studies. Secondly, as opposed to DNA, epigenetic profiles differ both between tissues and over time. This makes the choice of sample tissue to study critical, and poses challenges to the task of differentiating between epigenenetic variation as a cause of the disease *versus* consequence of the disease. In this respect, longitudinal study designs addressing exposures, changes in epigenetic states and disease development are needed.

Epigenetic mechanisms

Epigenetic phenomena are mediated by a variety of molecular mechanisms (fig. 3) [79]. The best studied mechanism is DNA methylation, which is the only known epigenetic modification of DNA itself in mammals [80]. The predominant form of DNA methylation is methylation of cytosines at position C5 in the context of cytosine-guanine (CpG) dinucleotides. It has also been recently suggested that CpH methlylation (where H=C/A/T) and 5-hydroxymethylation of cytosines are more common than previously appreciated, but the significance of this is still unclear [78]. CpG dinucleotides are generally under-represented in the mammalian genome (1–2%), but tend to cluster in regions called CpG islands, which contain >50% of cytosine and guanine nucleotides and are frequently located in gene promoter regions [81]. Hypermethylation of promoter CpG islands is commonly associated with transcriptional silencing, possibly by blocking the ability of transcription factors to bind to recognition sites on the CpG nucleotides, or by facilitating the binding of transcription-inhibiting proteins.

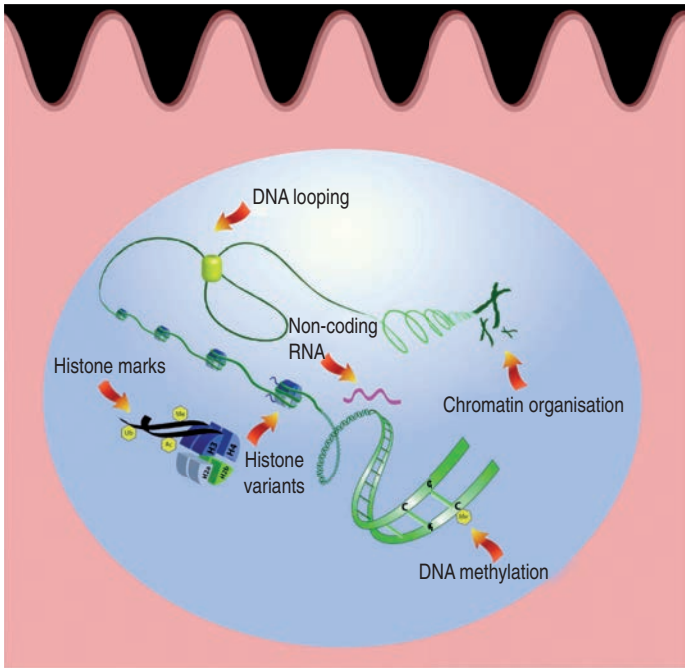

Figure 3. Epigenetic mechanisms: DNA methylation, histone modifications, non-coding RNA (microRNA) chromatin organisation. Reproduced from [79] with permission from the publisher.

DNA methylation is closely linked to another epigenetic mechanism, namely histone modifications. DNA is coiled around histone octamers, and organised into nucleosomes. Post-translational histone modifications, such as acetylation, methylation, ubiquitylation

and phosphorylation of histone amino-acid tails, are key elements in the packaging of DNA [82]. It is believed that such modifications lead to a remodelling of the promoter chromatin, determining how "easily" the DNA is available for gene transcription. It has further been found that unique repressive histone markers are associated with methylated promoters [83], while activating histone markers are associated with unmethylated promoters, illustrating the closely tuned epigenetic regulatory network.

Yet another level of epigenetic regulation is miRNAs. They are a class of small non-coding RNAs that may be transcribed from their own genes or introns/exons of other genes. By binding to target mRNAs, they degrade or modify target mRNAs and may also specifically inhibit protein translation [84]. An elegant example of miRNA regulation is that of the reproductive state in honey bees [85]. In these bees, fertile queens and sterile workers are alternative forms of the adult female honey bee that develop from genetically identical larvae following differential feeding with royal jelly. The study showed that honey bees treated with specific miRNAs, independently of royal jelly, also emerged as queens with fully developed ovaries. It is further known that one miRNA can target hundreds of mRNAs, and that one mRNA can be regulated by different miRNAs, illustrating a complex epigenetic regulatory system on the post-transcriptional level.

Thus, these major epigenetic mechanisms collectively affect interactions between DNA and transcriptional factors, DNA folding, chromatin compaction, transcript stability and nuclear organisation in a manner that determines if a gene is expressed or not.

Relationship between environment, genes and epigenetics

Over the past decade, studies have shown that genetic variations contribute to epigenetic modifications. There are studies suggesting that loci harbouring genetic variants exist that directly influence methylation states [86]. In addition, much has been learnt about the role of DNA methyltransferases (DNMTs), where DNMT1 facilitates the replication of DNA methylation patterns between cell generations (maintenance methylation), while DNMT2a and DNMT3b mediate *de novo* methylation of DNA [87]. Similarly, histones are modified by specific enzymes that include histone acetyltransferases (HAT), histone deacetylases (HDAC), histone methylases (HMTs) and histone demethylases (HDMTs). Genetic mutations or variations in these key enzymes have been linked to several different diseases and syndromes [88–91].

In addition to genetics, environmental exposures are increasingly being linked to epigenetic variation. A classic study by MORGAN *et al.* [76] showed that environmental factors lead to epigenetic changes in an animal model; the agouti mouse. In these mice, fur colour and proneness towards particular diseases were caused by variable expression of a particular gene at the agouti locus, which in turn was determined by the extent to which this gene was methylated. MORGAN *et al.* [76] were able to show that a diet enriched in folic acid increased the level of methylation of the gene and, thus, demonstrated that environmental agents can directly influence genomic structure and, ultimately, phenotype (in this case, fur colour). Recent studies in humans have also suggested environmental effects on DNA methylation: pre-natal tobacco exposure has been associated with differences in both gene-specific methylation and global DNA methylation (measured by methylation of long interspersed nucleotide element (LINE)-1 and Alu repetitive elements) [92]; pre-natal exposure to maternal depression has been shown to reduce neonatal methylation of the human glucocortiocoid receptor gene (*NR3C1*) and infant cortisol stress responses [93]; famine around the period of conception has been associated with lower DNA methylation at the imprinted *IGF2* gene [94]; and traffic particle exposure has been related to decreased global DNA methylation (LINE-1 and Alu repetitive elements) [95]. In addition, sufficient and balanced quantities of several dietary molecules, such as folic acid, vitamin B12, choline, betaine and niacin, are important for the establishment and maintenance of epigenetic modifications throughout the genome [96]. These complex interactions between environment, genes and epigenetics are illustrated by data showing that DNA methylation levels correlated with the levels of available folate and with genotype-dependent activity of the enzymes involved in DNA

methylation [97]. Thus, several environmental factors that are important in asthma have been linked to epigenetic changes, but this has not been linked to disease development to date.

The role of epigenetics in asthma

As previously discussed, asthma is considered to be a heterogeneous complex disease consisting of airway inflammation, characterised by airway infiltration of polarised CD4+ Th2 or Th17 cells in active interaction with dendritic cells, epithelial cells and macrophages [98]. Genetic studies suggest that asthma genes interact in complex manners to regulate the risk and severity of disease. Moreover, genetic studies published to date have not been able to fully explain the heritability of complex disease such as asthma. With better understanding of epigenetic mechanisms there is now an increased focus on possible epigenetic influences on asthma.

Epigenetic regulation on T-cell differentiation and inflammation

The asthmatic inflammatory response is characterised by the differentiation of naïve Th cells into primarily Th2 cells, expressing the cytokines IL-4, IL-5 and IL-13, as well as the reduced Th1-expressed interferon (IFN)-γ. Although it may, in certain cases, be difficult to differentiate between causal epigenetic mechanisms *versus* epigenetic changes as a result of disease, there is now mounting evidence of epigenetic mechanisms both preceding and underlying this T-cell differentiation, as extensively reviewed by WILSON *et al.* [99]. Examples include studies that show that the increased IL-4 expression is preceded and maintained by a demethylation of a transcriptional binding site in the *IL-4* gene [100], as well as a gain of activating histone markers in the IL-4 locus [85]. This is accompanied by repressive histone markers [101] and increased methylation [102] in the *IFN-γ* gene locus. Other indirect examples of epigenetic influence on asthmatic airways include a study showing that upregulation of specific HDACs restored steroid responsiveness in the airways of glucocorticoid-resistant asthmatics [103], and studies showing that treatment with specific HDAC inhibitors induce T-regulator cells and their suppressive functions on Th2-mediated allergic responses [98]. Thus, epigenetic studies suggest that the development of an inflammatory airway response is, at least in part, a result brought about by multiple, co-regulatory epigenetic changes on genes regulating T-cell differentiation.

Environmental influences on the epigenetic regulatory mechanisms

The understanding of epigenetic impact on inflammation raises the fundamental question about whether environmental influences on asthma are mediated through similar epigenetic pathways as discussed above. There has also been much speculation on whether or not epigenetics can help explain the previously discussed gene–environment interactions. Some of the latest studies addressing these issues will be reviewed here.

The pre-natal period is a time when epigenetic programming may lead to generations of cells with broad potential, and growing scientific evidence has supported a role for intrauterine environmental influences in the risk for later paediatric asthma [7]. An important question is whether maternal exposure has the capacity to activate or silence fetal genes through alterations in DNA and histone methylation, histone acetylation and chromatin structure. The most notable candidate to emerge in this role has been dietary folate. Folate is a methyl donor, and has been clearly associated with methylation changes in T-cell differentiation genes and subsequent increased risk of asthma and allergies in offspring in murine models [104]. Folic acid supplements during pregnancy have been associated with wheeze at 18 months of age in a large (>30,000) birth cohort study in Norway [105], as well as with risk of childhood asthma at 3.5 years and persistent asthma in an Australian birth cohort study [106]. A follow-up case–control study within the Norwegian birth cohort later detected an association between high folic acid levels in maternal plasma folate levels during pregnancy and an increased risk of childhood asthma at 3 years of age [107]. Animal studies further provide evidence that the allergy protective effects of microbial exposure in pregnancy may be mediated by changes in methylation of Th1 genes of the offspring [7].

Another recent small study links pre-natal pulmonary arterial hypertension exposure (polycyclic aromatic hydrocarbons) to methylation at the *ACSL3* gene and asthma in children before the age of 5 years [108]. The *ACSL3* gene belongs to the acyl-CoA synthetase long-chain family of genes encoding enzymes that are involved in fatty acid metabolism, and possibly influence membrane phospholipid composition. Furthermore, ACSL3 is expressed in lung and thymic tissue, and is located on 2q36.1 which is a region previously linked to lung function [109]. It has also been shown that pre-natal tobacco exposure affects global and gene-specific DNA methylation [92], but it remains to be seen whether these methylation changes affect the risk of asthma. Collectively, these studies support the idea that environmental conditions in the pre-natal period may in fact affect epigenetic programming and subsequent risk of disease, opening up the possibility of the identification of novel causal pathways and a better understanding of contributing environmental factors during pregnancy.

There is also evidence suggesting that environmental factors may modulate epigenetic regulation later in life. The most consistent environmental risk factor for asthma, after the pre-natal period, is the exposure to tobacco smoke. It is now becoming increasingly evident that tobacco exposure does affect the degree of DNA methylation and histone modifications in the genome. Bronchial lavage cells from smokers and nonsmokers have been compared, and differences have been found in HDAC3 mediated activity and the association to secretion of inflammatory cytokines [110]. In cancer research, smoking has been found to induce epigenetic changes in oncogenes and tumour suppressor genes, illustrated by the epigenetic silencing of the p16 gene (tumour suppressor gene) in small cell lung cancer [111], but the relevance of this to asthma is still unclear.

Other environmental candidates in relation to asthma are traffic particles, microbial products and allergens. Exposure to black carbon (from cars) has been associated with global DNA methylation over short periods (7 days) [95], but the relationship to asthma is still unclear. Combined inhaled diesel exhaust particles and allergen exposure have been shown to alter methylation of Th genes (inducing hypermethylation of the INF-γ promoter and hypomethylation of the IL-4 promoter) and IgE production *in vivo* [112]. Endotoxin (a compound of Gram-negative bacterial cells) has been implicated in many asthma gene (*CD14*)-environment interaction studies [113], and there are studies suggesting that endotoxin-induced tolerance is mediated through miRNAs [114]. Methylation of the *CD14* gene has also been shown to increase throughout childhood, suggesting modification of genetic impact with age [115]. House dust mite (HDM) antigens lead to the induction of allergic disease *in vivo*, which has been associated with the expression of a unique subset of miRNAs. Selective blockade of these miRNAs has been further shown to suppress the asthmatic phenotype in mice [116]. At present, there are few studies on humans; however, a study of miRNA profiles in human airway biopsies showed that miRNA expression was not involved in the development of mild asthma or in the anti-inflammatory action of the corticosteroid budesonide [117].

Thus, the increasing number of studies suggesting that environmental factors influence epigenetic modifications, and indirect evidence supporting the fact that these modifications are known to regulate genes central to the asthmatic inflammatory phenotype show that studies designed to and aimed at directly linking environment-epigenome-asthma phenotypes are clearly warranted.

Future perspectives in epigenetics

The growing field of epigenetics offers new and exciting insights into the intricate biology of asthma inflammation and T-cell differentiation, and is undoubtedly implicated in several observed complex gene and environment interactions. Not only might the understanding of epigenetic mechanisms reveal novel causal pathways, but it may lead to the identification of new anti-inflammatory treatments (such as targeting histone acetylation or miRNA suppression). However, epigenetic patterns, as opposed to genetic sequences, are both cell-type specific and dynamic through time-periods; rendering epigenetic regulation flexible yet posing specific research challenges. When are the critical time-points for epigenetic programming in terms of asthma

development? How can we differentiate causal epigenetic changes from those that are a consequence of disease? Which tissue should one use to study asthma epigenetics? How long do epigenetic memories last? Are they reversible by life-time events, environmental factors or epigenetic therapies? What side-effects will targeting methylation/histone modifications/miRNA in airways have on other organs? As epigenetic studies are still at a very early stage, these are some of the many questions that need to be addressed in the future design of epigenetic-asthma studies in order to delineate the role and clinical consequences of epigenetic modifications in this complex disease.

Conclusion

Genetic studies on asthma have provided us with new pathways which may be important in the development/pathogenesis of asthma, *e.g.* the role of epithelium-mesenchymal interaction and the role of epithelial integrity of the skin in preceding inflammation. Epigenetic modification may be important in switching asthma susceptibility genes on or off and, thus, influencing the development and/or severity of asthma. In addition, epigenetic modification can be influenced by environmental factors such as folate, smoke and HDM and, thus, interact between genetic and environmental factors.

Further research is needed to investigate the function of the discovered genes and their interaction with other genes and the environment, including the role of epigenetics. This may finally elucidate the pathogenesis of asthma and identify susceptible subjects to enable early-life screening, to contribute to (preventative) interventions and even prevent the disease.

Statement of Interest

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References

1. Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. *Eur Respir J* 2007; 29: 233–239.
2. World Health Organization. Global surveillance, Prevention and Control of Chronic Respiratory Diseases: a Comprehensive Approach. www.who.int/gard/publications/GARD_Manual/en/index.html Date last updated: 2007. Date last accessed: August 1, 2011.
3. Holgate S, Bisgaard H, Bjermer L, *et al.* The Brussels Declaration: the need for change in asthma management. *Eur Respir J* 2008; 32: 1433–1442.
4. Holgate ST, Arshad HS, Roberts GC, *et al.* A new look at the pathogenesis of asthma. *Clin Sci (Lond)* 2009; 118: 439–450.
5. Adcock IM, Ford P, Ito K, *et al.* Epigenetics and airways disease. *Respir Res* 2006; 7: 21.
6. Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest* 2011; 139: 640–647.
7. Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions *in utero. Curr Opin Allergy Clin Immunol* 2009; 9: 417–426.
8. Postma DS, Kerkhof M, Boezen HM, *et al.* Asthma and chronic obstructive pulmonary disease: common genes, common environments? *Am J Respir Crit Care Med* 2011; 183: 1588–1594.
9. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006; 7: 95–100.
10. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008; 8: 169–182.
11. Holloway JW, Koppelman GH. Identifying novel genes contributing to asthma pathogenesis. *Curr Opin Allergy Clin Immunol* 2007; 7: 69–74.
12. Holloway JW, Koppelman GH. 17q21 variants and asthma – questions and answers. *N Engl J Med* 2008; 359: 2043–2045.
13. Howard TD, Koppelman GH, Xu J, *et al.* Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 2002; 70: 230–236.
14. Kabesch M, Schedel M, Carr D, *et al.* IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006; 117: 269–274.

15. Simpson A, Maniatis N, Jury F, *et al.* Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-life lung function. *Am J Respir Crit Care Med* 2005; 172: 55–60.
16. Simpson A, Martinez FD. The role of lipopolysaccharide in the development of atopy in humans. *Clin Exp Allergy* 2010; 40: 209–223.
17. Smith FJ, Irvine AD, Terron-Kwiatkowski A, *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; 38: 337–342.
18. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38: 441–446.
19. McLean WH. The allergy gene: how a mutation in a skin protein revealed a link between eczema and asthma. *F1000 Med Rep* 2011; 3: 2.
20. O'Regan GM, Sandilands A, McLean WH, *et al.* Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2009; 124: R2–R6.
21. Holloway JW, Yang IA, Holgate ST. Genetics of allergic disease. *J Allergy Clin Immunol* 2010; 125: Suppl. 2, S81–S94.
22. Bouzigon E, Forabosco P, Koppelman GH, *et al.* Meta-analysis of 20 genome-wide linkage studies evidenced new regions linked to asthma and atopy. *Eur J Hum Genet* 2010; 18: 700–706.
23. Van Eerdewegh P, Little RD, Dupuis J, *et al.* Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002; 418: 426–430.
24. Moffatt MF. Genes in asthma: new genes and new ways. *Curr Opin Allergy Clin Immunol* 2008; 8: 411–417.
25. Blakey J, Halapi E, Bjornsdottir US, *et al.* Contribution of ADAM33 polymorphisms to the population risk of asthma. *Thorax* 2005; 60: 274–276.
26. Howard TD, Postma DS, Jongepier H, *et al.* Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. *J Allergy Clin Immunol* 2003; 112: 717–722.
27. Reijmerink NE, Kerkhof M, Koppelman GH, *et al.* Smoke exposure interacts with ADAM33 polymorphisms in the development of lung function and hyperresponsiveness. *Allergy* 2009; 64: 898–904.
28. Kere J, Laitinen T. Positionally cloned susceptibility genes in allergy and asthma. *Curr Opin Immunol* 2004; 16: 689–694.
29. Raby BA, Silverman EK, Kwiatkowski DJ, *et al.* ADAM33 polymorphisms and phenotype associations in childhood asthma. *J Allergy Clin Immunol* 2004; 113: 1071–1078.
30. Schedel M, Depner M, Schoen C, *et al.* The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. *Respir Res* 2006; 7: 91.
31. Jongepier H, Boezen HM, Dijkstra A, *et al.* Polymorphisms of the ADAM33 gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy* 2004; 34: 757–760.
32. van Diemen CC, Postma DS, Vonk JM, *et al.* A disintegrin and metalloprotease 33 polymorphisms and lung function decline in the general population. *Am J Respir Crit Care Med* 2005; 172: 329–333.
33. Puxeddu I, Pang YY, Harvey A, *et al.* The soluble form of a disintegrin and metalloprotease 33 promotes angiogenesis: implications for airway remodeling in asthma. *J Allergy Clin Immunol* 2008; 121: 1400–1406.
34. Haitchi HM, Powell RM, Shaw TJ, *et al.* ADAM33 expression in asthmatic airways and human embryonic lungs. *Am J Respir Crit Care Med* 2005; 171: 958–965.
35. Lee JY, Park SW, Chang HK, *et al.* A disintegrin and metalloproteinase 33 protein in patients with asthma: relevance to airflow limitation. *Am J Respir Crit Care Med* 2006; 173: 729–735.
36. Foley SC, Mogas AK, Olivenstein R, *et al.* Increased expression of ADAM33 and ADAM8 with disease progression in asthma. *J Allergy Clin Immunol* 2007; 119: 863–871.
37. Yang Y, Haitchi HM, Cakebread J, *et al.* Epigenetic mechanisms silence a disintegrin and metalloprotease 33 expression in bronchial epithelial cells. *J Allergy Clin Immunol* 2008; 121: 1393–1399.
38. Holgate ST, Yang Y, Haitchi HM, *et al.* The genetics of asthma: ADAM33 as an example of a susceptibility gene. *Proc Am Thorac Soc* 2006; 3: 440–443.
39. Haitchi HM, Bassett DJ, Bucchieri F, *et al.* Induction of a disintegrin and metalloprotease 33 during embryonic lung development and the influence of IL-13 or maternal allergy. *J Allergy Clin Immunol* 2009; 124: 590–597.
40. Chen C, Huang X, Sheppard D. ADAM33 is not essential for growth and development and does not modulate allergic asthma in mice. *Mol Cell Biol* 2006; 26: 6950–6956.
41. Moffatt MF, Kabesch M, Liang L, *et al.* Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007; 448: 470–473.
42. Hjelmqvist L, Tuson M, Marfany G, *et al.* ORMDL proteins are a conserved new family of endoplasmic reticulum membrane proteins. *Genome Biol* 2002; 3: RESEARCH0027.
43. Himes BE, Hunninghake GM, Baurley JW, *et al.* Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. *Am J Hum Genet* 2009; 84: 581–593.
44. DeWan AT, Triche EW, Xu X, *et al.* PDE11A associations with asthma: results of a genome-wide association scan. *J Allergy Clin Immunol* 2010; 126: 871–873.
45. Hancock DB, Romieu I, Shi M, *et al.* Genome-wide association study implicates chromosome 9q21.31 as a susceptibility locus for asthma in Mexican children. *PLoS Genet* 2009; 5: e1000623.
46. Sleiman PM, Flory J, Imielinski M, *et al.* Variants of DENND1B associated with asthma in children. *N Engl J Med* 2010; 362: 36–44.

47. Li X, Howard TD, Zheng SL, *et al.* Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. *J Allergy Clin Immunol* 2010; 125: 328–335.
48. Moffatt MF, Gut IG, Demenais F, *et al.* A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med 2010 23*, 363: 1211–1221.
49. Torgerson DG, Ampleford EJ, Chiu GY, *et al.* Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet* 2011; 43: 887–892.
50. Hirota T, Takahashi A, Kubo M, *et al.* Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. *Nat Genet* 2011; 43: 893–896.
51. Gudbjartsson DF, Bjornsdottir US, Halapi E, *et al.* Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet* 2009; 41: 342–347.
52. Ober C, Tan Z, Sun Y, *et al.* Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. *N Engl J Med* 2008; 358: 1682–1691.
53. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011; 242: 10–30.
54. Sleiman PM, Annaiah K, Imielinski M, *et al.* ORMDL3 variants associated with asthma susceptibility in north Americans of European ancestry. *J Allergy Clin Immunol* 2008; 122: 1225–1227.
55. Leung TF, Sy HY, Ng MC, *et al.* Asthma and atopy are associated with chromosome 17q21 markers in Chinese children. *Allergy* 2009; 64: 621–628.
56. Hirota T, Harada M, Sakashita M, *et al.* Genetic polymorphism regulating ORM1-like 3 (*Saccharomyces cerevisiae*) expression is associated with childhood atopic asthma in a Japanese population. *J Allergy Clin Immunol* 2008; 121: 769–770.
57. Halapi E, Gudbjartsson DF, Jonsdottir GM, *et al.* A sequence variant on 17q21 is associated with age at onset and severity of asthma. *Eur J Hum Genet* 2010; 18: 902–908.
58. Galanter J, Choudhry S, Eng C, *et al. ORMDL3* gene is associated with asthma in three ethnically diverse populations. *Am J Respir Crit Care Med* 2008; 177: 1194–1200.
59. Bouzigon E, Corda E, Aschard H, *et al.* Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008; 359: 1985–1994.
60. Smit LAM, Bouzigon E, Pin I, *et al.* 17q21 variants modify the association between early respiratory infections and asthma. *Eur Respir J* 2010; 36: 57–64.
61. Lluis A, Schedel M, Liu J, *et al.* Asthma-associated polymorphisms in 17q21 influence cord blood *ORMDL3* and *GSDMA* gene expression and IL-17 secretion. *J Allergy Clin Immunol* 2011; 127: 1587–1594.
62. Verlaan DJ, Berlivet S, Hunninghake GM, *et al.* Allele-specific chromatin remodeling in the *ZPBP2/GSDMB/ORMDL3* locus associated with the risk of asthma and autoimmune disease. *Am J Hum Genet* 2009; 85: 377–393.
63. Kim SH, Cho BY, Park CS, *et al.* Alpha-T-catenin (*CTNNA3*) gene was identified as a risk variant for toluene diisocyanate-induced asthma by genome-wide association analysis. *Clin Exp Allergy* 2009; 39: 203–212.
64. Koppelman GH, Meyers DA, Howard TD, *et al.* Identification of PCDH1 as a novel susceptibility gene for bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2009; 180: 929–935.
65. Xiao C, Puddicombe SM, Field S, *et al.* Defective epithelial barrier function in asthma. *J Allergy Clin Immunol* 2011; 128: 549–556.
66. Davies DE. The role of the epithelium in airway remodeling in asthma. *Proc Am Thorac Soc* 2009; 6: 678–682.
67. Taylor JM, Street TL, Hao L, *et al.* Dynamic and physical clustering of gene expression during epidermal barrier formation in differentiating keratinocytes. *PLoS One* 2009; 4: e7651.
68. Koning H, Sayers I, Stewart CE, *et al.* Characterization of protocadherin-1 expression in primary bronchial epithelial cells: association with epithelial cell differentiation. *FASEB J* 2012; 26: 439–448.
69. Barton SJ, Koppelman GH, Vonk JM, *et al.* PLAUR polymorphisms are associated with asthma, PLAUR levels, and lung function decline. *J Allergy Clin Immunol* 2009; 123: 1391–1400.
70. Ober C, Butte AJ, Elias JA, *et al.* Getting from genes to function in lung disease: a National Heart, Lung, and Blood Institute workshop report. *Am J Respir Crit Care Med* 2010; 182: 732–737.
71. Murphy A, Chu JH, Xu M, *et al.* Mapping of numerous disease-associated expression polymorphisms in primary peripheral blood CD4+ lymphocytes. *Hum Mol Genet* 2010; 19: 4745–4757.
72. Zhernakova A, Stahl EA, Trynka G, *et al.* Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet* 2011; 7: e1002004.
73. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. *Cell* 2007; 128: 635–638.
74. Bird A. Perceptions of epigenetics. *Nature* 2007; 447: 396–398.
75. Feinberg AP. Epigenetics at the epicenter of modern medicine. *JAMA* 2008; 299: 1345–1350.
76. Morgan HD, Sutherland HG, Martin DI, *et al.* Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet* 1999; 23: 314–318.
77. Rassoulzadegan M, Grandjean V, Gounon P, *et al.* RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. *Nature* 2006; 441: 469–474.
78. Rakyan VK, Down TA, Balding DJ, *et al.* Epigenome-wide association studies for common human diseases. *Nat Rev Genet* 2011; 1: 529–541.
79. Hernandez-Vargas H, Sincic N, Ouzounova M, *et al.* Epigenetic signatures in stem cells and cancer stem cells. *Epigenomic* 2009; 1: 261–280.

80. Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev* 2002; 16: 6–21.
81. Bogdanovic O, Veenstra GJ. DNA methylation and methyl-CpG binding proteins: developmental requirements and function. *Chromosoma* 2009; 118: 549–565.
82. Kouzarides T. Chromatin modifications and their function. *Cell* 2007; 128: 693–705.
83. Tiwari VK, McGarvey KM, Licchesi JD, *et al.* PcG proteins, DNA methylation, and gene repression by chromatin looping. *PLoS Biol* 2008; 6: 2911–2927.
84. Cannell IG, Kong YW, Bushell M. How do microRNAs regulate gene expression? *Biochem Soc Trans* 2008; 36: 1224–1231.
85. Kucharski R, Maleszka J, Foret S, *et al.* Nutritional control of reproductive status in honeybees *via* DNA methylation. *Science* 2008; 319: 1827–1830.
86. Zhang D, Cheng L, Badner JA, *et al.* Genetic control of individual differences in gene-specific methylation in human brain. *Am J Hum Genet* 2010; 86: 411–419.
87. Hermann A, Gowher H, Jeltsch A. Biochemistry and biology of mammalian DNA methyltransferases. *Cell Mol Life Sci* 2004; 61: 2571–2587.
88. Drini M, Wong NC, Scott HS, *et al.* Investigating the potential role of genetic and epigenetic variation of DNA methyltransferase genes in hyperplastic polyposis syndrome. *PLoS One* 2011; 6: e16831.
89. Fan H, Liu D, Qiu X, *et al.* A functional polymorphism in the DNA methyltransferase-3A promoter modifies the susceptibility in gastric cancer but not in esophageal carcinoma. *BMC Med* 2010; 8: 12.
90. Pasqualucci L, Dominguez-Sola D, Chiarenza A, *et al.* Inactivating mutations of acetyltransferase genes in B-cell lymphoma. *Nature* 2011; 471: 189–195.
91. Xu GL, Bestor TH, Bourc'his D, *et al.* Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene. *Nature* 1999; 402: 187–191.
92. Breton CV, Byun HM, Wenten M, *et al.* Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. *Am J Respir Crit Care Med* 2009; 180: 462–467.
93. Oberlander TF, Weinberg J, Papsdorf M, *et al.* Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* 2008; 3: 97–106.
94. Heijmans BT, Tobi EW, Stein AD, *et al.* Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA* 2008; 105: 17046–17049.
95. Baccarelli A, Wright RO, Bollati V, *et al.* Rapid DNA methylation changes after exposure to traffic particles. *Am J Respir Crit Care Med* 2009; 179: 572–578.
96. Kabesch M, Michel S, Tost J. Epigenetic mechanisms and the relationship to childhood asthma. *Eur Respir J* 2010; 36: 950–961.
97. Friso S, Choi SW, Girelli D, *et al.* A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proc Natl Acad Sci USA* 2002; 99: 5606–5611.
98. Ho SM. Environmental epigenetics of asthma: an update. *J Allergy Clin Immunol* 2010; 126: 453–465.
99. Wilson CB, Rowell E, Sekimata M. Epigenetic control of T-helper-cell differentiation. *Nat Rev Immunol* 2009; 9: 91–105.
100. Lee DU, Agarwal S, Rao A. Th2 lineage commitment and efficient IL-4 production involves extended demethylation of the IL-4 gene. *Immunity* 2002; 16: 649–660.
101. Wei G, Wei L, Zhu J, *et al.* Global mapping of H3K4me3 and H3K27me3 reveals specificity and plasticity in lineage fate determination of differentiating CD4+ T cells. *Immunity* 2009; 30: 155–167.
102. Jones B, Chen J. Inhibition of IFN-γ transcription by site-specific methylation during T helper cell development. *EMBO J* 2006; 25: 2443–2452.
103. Ito K, Chung KF, Adcock IM. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 2006; 117: 522–543.
104. Hollingsworth JW, Maruoka S, Boon K, *et al. In utero* supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest* 2008; 118: 3462–3469.
105. Haberg SE, London SJ, Stigum H, *et al.* Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child* 2009; 94: 180–184.
106. Whitrow MJ, Moore VM, Rumbold AR, *et al.* Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *Am J Epidemiol* 2009; 170: 1486–1493.
107. Haberg SE, London SJ, Nafstad P, *et al.* Maternal folate levels in pregnancy and asthma in children at age 3 years. *J Allergy Clin Immunol* 2011; 127: 262–264.
108. Burton A. Children's health: methylation links prenatal PAH exposure to asthma. *Environ Health Perspect* 2009; 117: A195.
109. Bouzigon E, Siroux V, Dizier M-H, *et al.* Scores of asthma and asthma severity reveal new regions of linkage in EGEA study families. *Eur Respir J* 2007; 30: 253–259.
110. Ito K, Lim S, Caramori G, *et al.* Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001; 15: 1110–1112.
111. Yanagawa N, Tamura G, Oizumi H, *et al.* Frequent epigenetic silencing of the p16 gene in non-small cell lung cancers of tobacco smokers. *Jpn J Cancer Res* 2002; 93: 1107–1113.

112. Liu J, Ballaney M, Al-alem U, *et al.* Combined inhaled diesel exhaust particles and allergen exposure alter methylation of T helper genes and IgE production *in vivo*. *Toxicol Sci* 2008; 102: 76–81.
113. Martinez FD. CD14, endotoxin, and asthma risk: actions and interactions. *Proc Am Thorac Soc* 2007; 4: 221–225.
114. Nahid MA, Pauley KM, Satoh M, *et al.* miR-146a is critical for endotoxin-induced tolerance: implication in innate immunity. *J Biol Chem* 2009; 284: 34590–34599.
115. Munthe-Kaas MC, Torjussen TM, Gervin K, *et al.* CD14 polymorphisms and serum CD14 levels through childhood: a role for gene methylation? *J Allergy Clin Immunol* 2010; 125: 1361–1368.
116. Mattes J, Collison A, Plank M, *et al.* Antagonism of microRNA-126 suppresses the effector function of TH2 cells and the development of allergic airways disease. *Proc Natl Acad Sci USA* 2009; 106: 18704–18709.
117. Williams AE, Larner-Svensson H, Perry MM, *et al.* MicroRNA expression profiling in mild asthmatic human airways and effect of corticosteroid therapy. *PLoS One* 2009; 4: e5889.

Chapter 10

The role of viral and bacterial infections on the development and exacerbations of asthma

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SUMMARY: A considerable proportion of asthma morbidity, mortality and health costs are attributed to asthma exacerbations. Epidemiological studies have convincingly shown that viral respiratory infections are the major causes of asthma exacerbations in both adults and children. Viruses, rhinoviruses in particular, infect the airway epithelium resulting in local and systemic immune responses as well as neural responses, inducing inflammation and airway hyperresponsiveness (AHR). The effects of an infection may vary according to genetic background, the current immune status of the host and parallel environmental stimuli, in addition to the particular infectious agent itself. Moreover, several studies have emphasised the importance of atopy and allergic inflammation in the induction and prolongation of virus-induced respiratory diseases. Identification of the mechanisms involved in the pathogenesis of asthma exacerbations and asthma persistence should facilitate development of future treatments tailored to the underlying cause.

KEYWORDS: Asthma, bacteria, exacerbations, virus

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In recent years, a growing number of observations have highlighted the importance of respiratory infections in acute asthma exacerbations (AAEs). Although a considerable proportion of asthma morbidity, mortality and health costs can be attributed to exacerbations, objective criteria for defining such events are lacking and it is sometimes difficult to differentiate an exacerbation from poor asthma control [1–4]. The Global Initiative for Asthma (GINA) guidelines define exacerbations as episodes of progressive shortness of breath, cough, wheezing or chest tightness, or a combination of these symptoms [5]. A joint task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) has recently defined asthma

exacerbations as events characterised by a change from the patient's previous status [3]. Moderate exacerbations are characterised as events troublesome to the patient that prompt a change in treatment and that are outside the patient's usual range of day-to-day asthma variation, although such an exacerbation is difficult to differentiate from poor asthma control requiring additional treatment. Mild exacerbations were not defined in the aforementioned task force because such events can be indistinguishable from loss of asthma control. From a paediatric perspective, these definitions are more difficult to use, taking into account the dependence on parental reporting, as well as the variability among childhood age groups. Nevertheless, the clinical experience of acute asthma worsening preceded by a common cold is overwhelming in paediatrics, and has been confirmed by many epidemiological studies.

With the advent of powerful detection methods, such as PCR, and detailed analysis of epidemiological data, our understanding of the implication of viral infections in AAEs has increased [6]. On some occasions, particularly in young children, common colds are unique precipitants of wheezing and associated symptoms. However, several conceptual issues have to be taken into account as the effects of an infection may vary according to genetic background, current immune status of the host and parallel environmental stimuli, in addition to the particular infectious agent itself. Interestingly, these effects can be non-linear, having even completely opposite results at different exposure levels [7].

It is well established that the major cause of asthma-related morbidity and mortality are AAEs and current asthma treatments are only partially effective at preventing AAEs [8]. Highlighting the pathways of the pathogenesis of asthma inception and virus-induced asthma exacerbations may have implications on designing and selecting optimal therapeutic strategies, in addition to indirectly affecting immunisation programmes, antibiotic use and antiviral drugs, as well as the development of new approaches to therapy.

Nevertheless, there is still some apparently contradictory information in respect to infections and asthma initiation and many unexplored aspects still need to be addressed [9]. The mechanisms by which respiratory infections exacerbate asthma in certain individuals are still not completely understood. At present, the possibility that some viral or intracellular bacterial infections may initiate asthma is being debated. It is possible that severe early viral infections play a causative role in the development of asthma by immune modulation, airway damage or both, or equally so that children who present with virus-induced wheezing have a predisposition. However, such suggestions may not be mutually exclusive.

This chapter will present current evidence on the associations between respiratory infections, asthma persistence and exacerbations of established asthma.

Epidemiology of virus-induced asthma exacerbations

The clinical experience of acute asthma worsening preceded by a common cold is old and overwhelming in paediatrics; it has also been confirmed by many epidemiological studies. The first studies investigating the specific viral aetiology of acute wheezing/asthma in children were performed 40 years ago, but because of the limited sensitivity of the methods used the frequency of viral detection ranged from 14% to 49% [10].

With the development of sensitive methodologies for the detection of the most prevalent respiratory viruses, such as rhinoviruses and corona viruses, researchers were able to demonstrate stronger associations between common viral respiratory infections and asthma exacerbations. Paediatric studies were able to identify respiratory viruses in 62–95% of wheezing children (with more cases reporting a prevalence of >80%) in both community and hospital settings [11].

Rhinoviruses are the most prevalent viruses detected in all age groups (60% of asthma exacerbations) and, in fact, the only viruses statistically significantly associated with exacerbations in children (odds ratio 6.8), with the exception of infants hospitalised with bronchiolitis, where

respiratory syncytial virus (RSV) predominates [12–14]. However, a rapid decrease in the prevalence of RSV takes place thereafter; the breaking point in the predominance between rhinoviruses and RSV severe wheezing illnesses occurs at approximately 12 months of age in a setting of hospitalised children [15]. The prevalence in adults is also highly reported, although to a lesser extent (41–78%), probably because of pragmatic differences in the prevalence of virus-induced exacerbations or due to the fact that adults shed less infective virus [16, 17]. Interestingly, the peak of severe exacerbations in children occurs shortly after their return to school following the holidays and in adults 1 week later, coinciding with peaks in rhinovirus infections in autumn and, to a lesser extent, in spring [18]. A recently recognised rhinovirus species (RV-C) has been associated with increased severity of AAE in respect to other strains of rhinoviruses [19]. Certain concerns were raised regarding the clinical significance of a positive PCR for viruses in biological samples, since high virus detection rates were also found in asymptomatic children and, moreover, multiple coexisting viruses were identified in symptomatic individuals [20, 21]. However, studies taking into account and adjusting for asymptomatic carriage have confirmed that the PCR detection is more likely to reflect true clinical or at least subclinical infection [22].

Rhinovirus epidemiology is complex; up to 20 strains circulate during a single season and the prevailing rhinovirus strains differ according to season and location and almost completely change from year to year [23]. Respiratory symptoms typically develop after 1–2 days in inoculation studies and, if uncomplicated, resolve by 1 week post-inoculation [24].

Other respiratory viruses associated with exacerbations display different seasonal variation; RSV and influenza are mostly present and associated with AAE during the winter months [25, 26]. Influenza viruses may trigger asthma exacerbations less frequently than other respiratory viruses [27]. Among the more recently identified viruses, human metapneumovirus has been associated with wheezing episodes, mostly in younger children, while human bocavirus accounts for ~5% of asthma exacerbations [28–31]. Other viruses such as coronavirus, adenovirus and parainfluenza have also been associated with AAE, although at lower rates [32].

Mycoplasma pneumoniae and *Chlamydophila pneumoniae* are found more frequently in the airways of patients with asthma in comparison to healthy controls; their role in exacerbations is less clear and hampered by methodological problems in their kinetics and identification [33]. In the majority of exacerbation studies looking for a wide array of pathogens, the relative proportion of atypical bacteria detection is low. Nevertheless, BISCARDI *et al.* [34] identified *M. pneumoniae* in 20% of exacerbations in asthmatic children requiring hospitalisation, while 50% of children experiencing their first asthmatic attack were also positive.

Recently, a systematic review has summarised current knowledge in microbial epidemiology of acute asthma in children and adults, as well as the prevalence of specific agents on asthma exacerbations (fig. 1) [35].

Although several studies have shown that AAE are strongly associated with respiratory tract infections and the term "virus-induced exacerbation" is not uncommon, only a small number of such studies are prospective [11, 16] and even fewer have simultaneously assessed other potential factors that may contribute towards the exacerbation [36]. Furthermore, respiratory infections do not always result in an exacerbation, as there is little evidence that treating or preventing the infection may cure or prevent an exacerbation. Therefore, a clear causal relationship is still to be established.

The role of early RSV infections on asthma development

It has been well established that RSV infections are a major trigger for wheeze in infants and young children [37]. In respect to asthma and/or atopy development, RSV bronchiolitis has been frequently implicated but causality has been just as frequently challenged [38]. There is now strong evidence, mainly from epidemiological studies, suggesting that RSV bronchiolitis is a

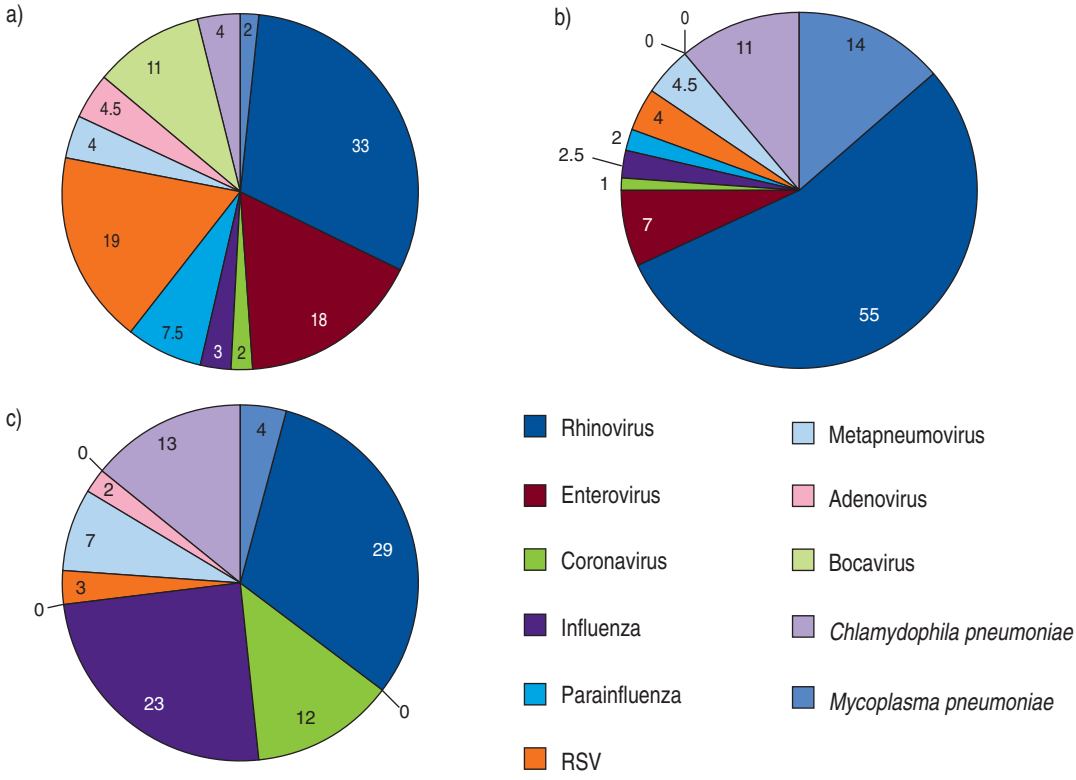

Figure 1. Reported prevalence of individual microbial agents in acute asthma exacerbations in a) infants and preschool children, b) children aged 6–17 years and c) adults. RSV: respiratory syncytial virus. Data from [15].

significant independent risk factor for subsequent wheezing, at least within the first decade, and for deficits in lung function but is not a risk factor for increased risk of atopy, at least not in all cases [39–41]. Moreover, a dose–response relationship between the severity of infant bronchiolitis and the risk for presenting asthma and asthma-specific morbidity at the age of 5 years has been demonstrated [42].

Another significant element that is supported by systematic studies in animal models and by more limited data from infants, and which probably plays a pivotal role on the immunological response to the initial and subsequent infections, is age at first RSV infection [43]. It has been shown that RSV infection is a predisposition to the development of inflammatory responses and altered lung function *via* altered T-helper cell (Th)2 responses, but only when the initial infection occurs at an early age [44]. Such responses have characteristics of a less mature immune system. There are now enough data indicating that events occurring early in life have a decisive influence on developmental trajectories which influence the subsequent development of asthma [45].

What remains unclear is the direction of causation, as previously stated [39, 41, 46]. Retrospective analysis of an interventional study with anti-RSV monoclonal antibody (palivizumab) in pre-term infants at high risk for RSV infection reported a 50% decrease in the incidence of recurrent wheeze during the first 3 years of life, positively associating RSV infection and subsequent wheezing illnesses [47]. In addition, it has been shown that children born in September carry a higher risk for asthma, probably because of an association with virus peak season, and are suggestive of virus seasonality as a risk factor for asthma development; however, these data contribute little to clarify causation [48]. Furthermore, epidemiological data from the Tucson study (AZ, USA) indicate that pre-morbid lung function predicts low lung function later in life that may not (at least not significantly) be affected by the RSV bronchiolitis event [49]. Using a large dataset of twin pairs in

Denmark it was proposed that the RSV–asthma correlation was essentially due to genetic effects shared between traits, although incomplete clinical characterisation of the study population and the infections determination make the interpretation difficult [50]. There is an essential need for randomised controlled prospective studies to evaluate the effectiveness of prevention of RSV-induced wheezing illnesses on asthma outcomes [51].

The role of rhinovirus infections on asthma development

Recent data highlight rhinovirus-induced wheezing in early years as an important risk factor for subsequent development of persistent wheeze/asthma, more so than RSV bronchiolitis. Studies from a recently described mouse model suggest that a single viral infection, in addition to the acute effects typically described, may result in the development of chronic inflammation, probably increasing the chances of a subsequent infection and/or exacerbation [52]. However, mouse models of rhinovirus infection have only recently been described and whether the above effects can be generalised is unknown [53].

The importance of early rhinovirus infections has also been reported in cohort studies. In a Finnish cohort of more than 100 infants (mean age 12 months) hospitalised for wheezing, rhinovirus identification was associated with a five-fold risk for subsequent wheezing compared to RSV cases during the subsequent 12 months [54]. Furthermore, a long-term, post-bronchiolitis follow-up study assessing the outcome in respect to asthma development after early childhood rhinovirus-induced wheezing reported that asthma was more prevalent following rhinovirus (52%) than RSV (15%) bronchiolitis [55]. In line with the previous study, prospective data further support the notion that the risk of wheezing is higher after non-RSV compared to RSV bronchiolitis within the following 3 years [56]. The extent of this association has been remarkable, with rhinovirus wheezing illnesses during the first 3 years of life increasing the risk of children presenting with asthma by the age of 6 years up to 40-fold, a much higher degree than allergen sensitisation or RSV infections [57]. In addition, the Childhood Asthma Study (CAS) has clearly shown that predominantly rhinovirus-induced wheezing in the first year of life was a significant risk factor for asthma occurrence by the age of 5 years; however, the aforementioned risk was restricted to those with allergic sensitisation by the age of 2 years [58].

Although no solid data exist on the effect of rhinovirus wheezing illnesses up to adulthood, there is substantial evidence that the aforementioned risk on asthma occurrence may persist at least until adolescence [59].

Several mechanisms have been proposed for the induction of asthma symptoms following respiratory infections. A causal role seems plausible, since the bronchial epithelium might be vulnerable to pathogens during early years of life when the respiratory and immune systems are still under maturation [24]. It is also possible that virus-induced wheezing reveals a predisposition towards asthma, secondary to impaired lung function. A third possibility has also been proposed, in which viral infections promote asthma, mainly in predisposed children [60, 61]. Nevertheless, many critical questions remain unanswered in respect to the possibility that one or more infections may drive inflammatory responses towards an unresolved state, including the role of specific microorganisms, the role of the immune system in controlling or resolving inflammation and, of course, the effects of additional synergistic, possibly subclinical, factors. In addition, the course of wheezing illness/asthma can vary widely over time. Patterns of remission, relapse and new disease development at any age suggest that the natural history of the disease may not be deterministic, *i.e.* ''decided'' at an early stage by either a genetic pattern or an environmental exposure, but rather indeterministic, *i.e.* continuously developing in relation to ongoing non-predictable exposures. According to this hypothesis, repeated, acute infection-mediated events may reprogramme the innate, adaptive and/or regulatory immune responses towards a chronic inflammation pattern. Evaluation of the latter hypothesis is currently being undertaken in the context of an EU-funded project, PreDicta (www.predicta.eu).

Mechanisms of virus-induced exacerbations

A wide range of mechanisms have been implicated in the progression from a viral respiratory infection to an acute exacerbation of asthma, and have recently been reviewed [62].

An integrated response, aimed at the efficient clearance of the virus, occurs during a respiratory infection. Elements of such response include the respiratory, immune and nervous system. The bronchial epithelium plays a pivotal role by serving as the site of viral replication [63] and participating in the initiation of several antiviral [64, 65], innate and adaptive immune, and inflammatory responses through the production of a wide array of cytokines and chemokines (fig. 1) [66]. Additionally, rhinovirus infection activates inflammatory pathways and increases levels of neutrophils, eosinophils, CD4+ cells, CD8+ cells and mast cells through increased mRNA expression and translation of, among others, interleukin (IL)-6, IL-8, IL-16, eotaxin, interferon (IFN)-γ-induced protein 10 (IP10) and CCL5 (RANTES) [67]. Equally importantly, an immune response is generated locally and systematically while neural signals are generated in response, or in an attempt, to control or coordinate the inflammation.

The time course of rhinovirus infection in AAE is still not completely understood. It has been shown that rhinoviruses may induce early viraemia, at least in more severe cases, and may persist for several weeks [68, 69], although this has been challenged by the possibility of frequent re-infections [22].

Structural cells and innate immune responses

The extent of epithelial cell destruction varies according to the type of virus. Influenza virus has been shown to cause extensive epithelial necrosis whereas rhinoviruses usually cause little or only patch epithelial damage. *In vitro* models have demonstrated that rhinovirus infection may modulate epithelial responses by delaying epithelial repair [70]. In addition, in the presence of an atopic environment, rhinovirus-induced epithelial responses are altered, reducing viral clearance and promoting cytotoxicity [71]. Rhinovirus infections have also been shown to promote airway remodelling by inducing angiogenesis, mediated through the vascular endothelial growth factor (VEGF), an effect also enhanced by the presence of atopy [72]. Similar responses were also observed for other pro-fibrotic factors, such as transforming growth factor (TGF)-β [71] and fibroblast growth factor (FGF)-2 [73]. These observations have been confirmed in studies reporting that rhinovirus infection of cultured epithelial cells results in upregulation of amphiregulin (a member of the epidermal growth factor family), activin (a member of the TGF-β family) and VEGF [74].

Innate immune responses, in particular IFNs, seem to play a major role in rhinovirus-induced asthma exacerbations. Bronchial epithelial cells (BECs) from atopic asthmatics have been shown to be profoundly deficient in producing rhinovirus-induced IFN-β and IFN-λ, resulting in increased rhinovirus replication, while exogenous IFN-β induced apoptosis of rhinovirus-infected asthmatic BECs and restoration of innate immunity by inhibiting rhinovirus replication [75, 76]. Deficiency of IFN-λ induction by rhinovirus was also observed in macrophages of atopic asthmatics, and this was related to increased virus load, asthma exacerbations and severity of asthma inflammation *in vivo* [76]. A more recent study demonstrated that IFN-L1 and not IFN-L2/3 mRNA levels obtained from sputum cells of moderate-to-severe asthmatics negatively correlated with asthma symptoms, highlighting the protective role of IFN-λ subypes in asthma [77]. In the same context, peripheral blood mononuclear cells (PBMCs) from asthmatic patients were reported to produce less IFN-α2 than PBMCs from normal controls in response to other viruses, such as RSV and the Newcastle virus, implicating IFN-α in the pathogenesis of AAE [78]. The complex impairment of anti-viral immune responses in asthmatics is further augmented by recent observations of decreased levels of IL-15, a cytokine implicated in the innate and acquired antiviral immunity, and inversely related to airway hyperresponsiveness (AHR) and virus load following rhinovirus infection [79]. It has been postulated that polymorphisms in genes encoding transcription factors or signalling

molecules essential for the expression of the IFNs may account for such deficiencies [80]. However, deficient IFN responses in asthmatics could not be confirmed in all studies, and moreover studies in experimentally inoculated volunteers failed to demonstrate significant differences in rhinovirus shedding in respect to asthma [81–83]. It is possible that differences in disease characteristics and/or the population included in the studies, as well as methodological differences, could account for such discrepancies; however, more studies are needed to clarify this point.

Neural mechanisms

Post-viral alterations in neural control include dysfunction of pre-junctional M2-muscarinic inhibitory receptors, which normally inhibit acetylcholine release, or the release of bronchoconstricting neuropeptides [84]. In addition, RSV infection induces changes in the mast cell-nerve synapses resulting in natural killer (NK)1 receptor upregulation and exacerbation of substance P-induced bronchoconstriction and smooth muscle contraction [62]. Viral infections can also upregulate neurotrophins that in turn control the development of the airway neural network [85]. Such an effect could alter bronchoconstrictive responses to nonspecific irritants, including future respiratory infections.

Virus–allergen interactions in asthma exacerbations and persistence

It is well accepted that a combination of interacting factors is likely to be involved in the pathogenesis of AAE. Studies performed during the last decade have emphasised the importance of atopy and allergic inflammation in the induction and perpetuation of virus-induced respiratory diseases [21, 86]. The issue of whether atopy *per se* alone could account for both symptoms and exacerbations of asthma is still being debated. The vast majority of clinical and *ex vivo* studies dealing with the underlying mechanisms of virus-induced exacerbations do not take into account that a significant proportion of asthmatics are not atopic, although recent data support the notion that airway cytopathology might not differ significantly between the two groups. Quantitative relationships have been shown between allergen sensitisation, as indicated by measures of specific immunoglobulin (Ig)E, and the likelihood of presenting with asthma-related symptoms [87]. Further analysis showed that the earlier the sensitisation, the more increased the risk of asthma development, suggesting that atopy is a potent aetiological factor for asthma occurrence [88]. The importance of atopy in the persistence of the asthmatic phenotype into adolescence is now well established [89].

Data deriving from rhinovirus experimental infection in asthmatics clearly showed enhanced lower respiratory symptoms, lung function impairment, a positive correlation of the virus load to augmented Th2 responses, and clinical outcomes in atopic asthmatics, suggesting a possible link among allergic sensitisation and rhinovirus infection [83]. In clinical settings of hospitalised individuals, allergens and respiratory viruses have been shown to act synergistically in the expression of severe asthma symptoms in adults and children [36, 90]. Furthermore, the sharp increase in emergency department visits for virus-induced asthma exacerbations in September has been postulated to be affected by aeroallergen concentrations and host responses [18]. In the community-based Western Australian Pregnancy Cohort, the risk of asthma increased approximately nine-fold for children who had both atopy by age 6 years and more than two wheezing-associated episodes in the first year of life. In those children, the degree of atopy was related to increased risk of subsequent asthma in a dose-dependent manner [60]. In a recent study where routine nasal secretion samples were obtained during rhinovirus high prevalence seasons, allergic sensitisation was associated with prolonged and more severe exacerbations in asthmatic children, although viral detection rates did not differ between groups [23]. From another point of view, and taking into account that the degree of AHR is an indirect marker of asthma severity and inflammation, it has been shown that although the duration of AHR after a single cold is not

affected by the atopic status of the patient, an increased number of colds results in prolonged AHR only in atopics, possibly contributing to perpetuation of inflammation and persistence of asthma symptomatology [21].

Allergens and viruses may act in a synergistic manner in damaging the airway epithelium. Viral infections, on the one hand, compromise the barrier function of the airway epithelium resulting in enhanced absorption of allergen and, on the other hand, *in vitro* rhinovirus replication is greater in disrupted epithelium, resembling the asthmatic, probably leading to more severe clinical illnesses [91, 92]. Data from animal models suggest that biased innate immune responses to respiratory viruses early in life possibly promote overproduction of key cytokines, such as IL-13, leading to suboptimal antiviral responses and increased risk of developing respiratory allergies and chronic lung diseases (CLD) [52]. *In vitro* models have shown that synergy between virus and mite (der p 1)-induced inflammation may also occur through combined nuclear factor (NF)-κB activation [93]. To further support this, a series of experimental respiratory infections in humans have suggested that viruses might act to enhance asthma lipid protein receptors (LPRs) through augmentation of underlying allergen-specific responses [94]. In line with the previous studies, a central role for Th2-associated IL-4/IL-13 pathways in the LPRs of atopic asthmatic subjects has been indicated [95]. More recently, data deriving from a study of children hospitalised due to AAE revealed a central role for members of the type-1 IFN and IL-4/IL-13 signalling pathways in circulating myeloid cells (monocytes and dendritic cells) from associated gene signatures [96]. Of interest, those myeloid cells exhibited high-level expression of CCR2, which has been identified as one of the major chemokine receptors involved in homing of inflammatory cells to inflamed airways, and were also IL-13 receptor positive [97]. Notably, both rhinoviris infection and allergic inflammation induce thymic stromal lymphopoietin (TLSP) deriving from epithelial cells, a cytokine that acts on dendritic cells enhancing Th2 differentiation [98]. The aforementioned data are highly suggestive of a virus-triggered type-1 IFN and IL-4/IL-13 being released from the airway mucosa into the circulation during acute exacerbation and being sensed by receptor-bearing myeloid precursors in bone marrow [99]. Based on this, an elegant theory on the induction and persistence of asthma symptoms in virally infected atopic children suggests that signals triggered during the innate immune response to the virus can lead to the release of large numbers of migrating high-affinity, IgE receptor-bearing, bone marrow-derived precursors of mucosal dendritic cells into the blood. The subsequent trafficking of these cells to the infected airway mucosa, where dendritic cell turnover is very high, provides a potential mechanism for recruitment of underlying aeroallergen-specific Th2 immunity into the already inflamed milieu of the infected airway mucosa [100].

Notably, the vast majority of clinical and *ex vivo* studies dealing with the underlying mechanisms of virus-induced exacerbations ignores the fact that many asthmatics are not atopic, although recent data support the notion that airway pathology does not differ significantly between the two groups [101]. To this respect, studies including non-atopic asthmatics and an effort to minimise reporting bias are needed.

Bacterial infections and asthma exacerbations

Infections caused by atypical bacteria, *i.e. M. pneumoniae* and *C. pneumoniae*, have been associated with exacerbations of asthma, as well as with persistence and severity of asthma [102, 103]. Most of the studies investigating the role of *M. pneumoniae* and *C. pneumoniae* (six in children) in acute asthma symptoms are indicative of a positive association [104–114]. Available evidence supports a role for acute *M. pneumoniae* and *C. pneumoniae* respiratory tract infections as a trigger for 5–30% of wheezing episodes and/or AAE [115]. However, *M. pneumoniae* and *C. pneumoniae* infections may also be accompanied by wheezing in children considered not to have asthma [116, 117]. In the general paediatric population the incidence of wheezing in acute *M. pneumoniae* infection was reported to be 25–40%, although the majority of the studies vary by population studied, due to variations in the definitions of wheeze and asthma [118]. BISCARDI *et al.* [34] found that *M. pneumoniae* was present in 20% of exacerbations in asthmatic children requiring

hospitalisation, but in 50% of children experiencing their first asthmatic attack. However, in some instances when PCR methods were used in hospitalised individuals, no significant associations between *M. pneumoniae* and *C. pneumoniae* infection and clinical illnesses were found, further contributing to the controversial role of atypical bacteria in acute asthma [103]. There are still unresolved issues both in respect to microorganism identification, as well as study design, before an aetiological association can be firmly established [33].

Several studies have assessed the role of *M. pneumoniae* and *C. pneumoniae* infection in the initiation of asthma, however, with conflicting findings. The presence of IgG antibodies to *C. pneumoniae* in subjects with late-onset non-atopic asthma was associated with significant declines in lung function measurements [119]. Moreover, experimental *M. pneumoniae* infection in a murine model has resulted in chronic pulmonary disease characterised by airway hyperreactivity, obstruction and histological inflammation [120]. However, other studies failed to verify such associations [121]. Evidence of a causal role of *M. pneumoniae* and *C. pneumoniae* in the initiation of asthma emerging from paediatric studies is inconsistent [34, 122]. Recently, it has been proposed that bacterial colonisation might be associated with both the initiation and the exacerbation of asthma. Colonisation of the upper airways with bacterial pathogens in infancy has been associated with an increased risk of presenting with asthma-associated symptoms later in life [123]. Moreover, in a prospective study from age 3 weeks to 4 years assessing the carriage of bacteria and virus during wheezing episodes, bacteria were found to be significantly associated with wheezing symptoms but similar to an independent manner of the association with viruses [124].

Although studies on the causation of asthma exacerbations exist, it is unclear whether safe conclusions can be drawn, since inclusion criteria vary significantly between studies. Furthermore, respiratory infections do not always result in an exacerbation, and there is little evidence that treating or preventing the infection may cure or prevent an exacerbation. The relative contribution of viruses and bacteria in asthma exacerbations, as well as their interactions, remain largely unknown. Although the limits of virus-associated asthma and exacerbations in children will continue to be scrutinised and debated, the majority of such events would be clinically indisputable.

Statement of Interest

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References

1. Johnston SL. Overview of virus-induced airway disease. *Proc Am Thorac Soc* 2005; 2: 150–156.
2. Taylor DR, Bateman ED, Boulet L-P, *et al.* A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008; 32: 545–554.
3. Reddel HK, Taylor DR, Bateman ED, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180: 59–99.
4. Reddel H, Ware S, Marks G, *et al.* Differences between asthma exacerbations and poor asthma control. *Lancet* 1999; 353: 364–369.
5. National Heart Lung and Blood Institute. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm Date last updated: September 2007.
6. Sykes A, Seemungal T. Recent advances in exacerbations of asthma. *Thorax* 2008; 63: 758–760.
7. Simpson A, Custovic A. Prevention of allergic sensitization by environmental control. *Curr Allergy Asthma Rep* 2009; 9: 363–369.
8. O'Byrne PM. Therapeutic strategies to reduce asthma exacerbations. *J Allergy Clin Immunol* 2011; 128: 257–263.
9. Xepapadaki P, Papadopoulos NG. Childhood asthma and infection: virus-induced exacerbations as determinants and modifiers. *Eur Respir J* 2010; 36: 438–445.
10. Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy* 1992; 22: 325–336.

11. Johnston SL, Pattemore PK, Sanderson G, *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310: 1225–1229.
12. Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005; 11: 21–26.
13. Khetsuriani N, Kazerouni NN, Erdman DD, *et al.* Prevalence of viral respiratory tract infections in children with asthma. *J Allergy Clin Immunol* 2007; 119: 314–321.
14. Everard ML. Acute bronchiolitis and croup. *Pediatr Clin North Am* 2009; 56: 119–133.
15. Jartti T, Lehtinen P, Vuorinen T, *et al.* Bronchiolitis: age and previous wheezing episodes are linked to viral etiology and atopic characteristics. *Pediatr Infect Dis J* 2009; 28: 311–317.
16. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993; 307: 982–986.
17. Westerly BD, Peebles RS Jr. Respiratory syncytial virus infections in the adult asthmatic – mechanisms of host susceptibility and viral subversion. *Immunol Allergy Clin North Am* 2010; 30: 523–539.
18. Johnston NW, Johnston SL, Norman GR, *et al.* The September epidemic of asthma hospitalization: school children as disease vectors. *J Allergy Clin Immunol* 2006; 117: 557–562.
19. Bizzintino J, Lee W-M, Laing IA, *et al.* Association between human rhinovirus C and severity of acute asthma in children. *Eur Respir J* 2010; 37: 1037–1042.
20. Jartti T, Jartti L, Peltola V, *et al.* Identification of respiratory viruses in asymptomatic subjects: asymptomatic respiratory viral infections. *Pediatr Infect Dis J* 2008; 27: 1103–1107.
21. Xepapadaki P, Papadopoulos NG, Bossios A, *et al.* Duration of postviral airway hyperresponsiveness in children with asthma: effect of atopy. *J Allergy Clin Immunol* 2005; 116: 299–304.
22. Jartti T, Lee W-M, Pappas T, *et al.* Serial viral infections in infants with recurrent respiratory illnesses. *Eur Respir J* 2008; 32: 314–320.
23. Olenec JP, Kim WK, Lee WM, *et al.* Weekly monitoring of children with asthma for infections and illness during common cold seasons. *J Allergy Clin Immunol* 2010; 125: 1001–1006.
24. Gavala ML, Bertics PJ, Gern JE. Rhinoviruses, allergic inflammation, and asthma. *Immunol Rev* 2011; 242: 69–90.
25. Bartlett NW, McLean GR, Chang YS, *et al.* Genetics and epidemiology: asthma and infection. *Curr Opin Allergy Clin Immunol* 2009; 9: 395–400.
26. Wright M, Piedimonte G. Respiratory syncytial virus prevention and therapy: past, present, and future. *Pediatr Pulmonol* 2011; 46: 324–347.
27. Jartti T, Ruuskanen O. Influenza virus and acute asthma in children. *Pediatrics* 2008; 121: 1079–1080.
28. Williams JV, Harris PA, Tollefson SJ, *et al.* Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004; 350: 443–450.
29. Foulongne V, Guyon G, Rodiere M, *et al.* Human metapneumovirus infection in young children hospitalized with respiratory tract disease. *Pediatr Infect Dis J* 2006; 25: 354–359.
30. Vallet C, Pons-Catalano C, Mandelcwajg A, *et al.* Human bocavirus: a cause of severe asthma exacerbation in children. *J Pediatr* 2009; 155: 286–288.
31. Xepapadaki P, Psarras S, Bossios A, *et al.* Human metapneumovirus as a causative agent of acute bronchiolitis in infants. *J Clin Virol* 2004; 30: 267–270.
32. Xepapadaki P, Papadopoulos NG. Viral infections and allergies. *Immunobiology* 2007; 212: 453–459.
33. Xepapadaki P, Papadopoulos NG. Atypical bacteria and macrolides in asthma. *Allergy Asthma Clin Immunol* 2008; 4: 111–116.
34. Biscardi S, Lorrot M, Marc E, *et al. Mycoplasma pneumoniae* and asthma in children. *Clin Infect Dis* 2004; 38: 1341–1346.
35. Papadopoulos NG, Christodoulou I, Rohde G, *et al.* Viruses and bacteria in acute asthma exacerbations – a GA(2)LEN-DARE systematic review. *Allergy* 2011; 66: 458–468.
36. Murray CS, Poletti G, Kebadze T, *et al.* Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006; 61: 376–382.
37. Newcomb DC, Peebles RS Jr. Bugs and asthma: a different disease? *Proc Am Thorac Soc* 2009; 6: 266–271.
38. Kuehni CE, Spycher BD, Silverman M. Causal links between RSV infection and asthma: no clear answers to an old question. *Am J Respir Critical Care Med* 2009; 179: 1079–1080.
39. Stein RT, Sherrill D, Morgan WJ, *et al.* Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; 354: 541–545.
40. Kusel MM, de Klerk NH, Holt PG, *et al.* Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2006; 25: 680–686.
41. Sigurs N, Gustafsson PM, Bjarnason R, *et al.* Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; 171: 137–141.
42. Carroll KN, Wu P, Gebretsadik T, *et al.* The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. *J Allergy Clin Immunol* 2009; 123: 1055–1061.
43. Papadopoulos NG, Kalobatsou A. Respiratory viruses in childhood asthma. *Curr Opin Allergy Clin Immunol* 2007; 7: 91–95.
44. Dakhama A, Park JW, Taube C, *et al.* The enhancement or prevention of airway hyperresponsiveness during reinfection with respiratory syncytial virus is critically dependent on the age at first infection and IL-13 production. *J Immunol* 2005; 175: 1876–1883.

45. Kuehni CE, Strippoli MP, Low N, *et al.* Asthma in young south Asian women living in the United Kingdom: the importance of early life. *Clin Exp Allergy* 2007; 37: 47–53.
46. Perez-Yarza EG, Moreno A, Lazaro P, *et al.* The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J* 2007; 26: 733–739.
47. Simoes EA, Groothuis JR, Carbonell-Estrany X, *et al.* Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007; 151: 34–42.
48. Wu P, Dupont WD, Griffin MR, *et al.* Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med* 2008; 178: 1123–1129.
49. Turner SW, Young S, Landau LI, *et al.* Reduced lung function both before bronchiolitis and at 11 years. *Arch Dis Child* 2002; 87: 417–420.
50. Thomsen SF, van der Sluis S, Stensballe LG, *et al.* Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009; 179: 1091–1097.
51. Stein RT, Martinez FD. Respiratory syncytial virus and asthma: still no final answer. *Thorax* 2010; 65: 1033–1034.
52. Kim EY, Battaile JT, Patel AC, *et al.* Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med* 2008; 14: 633–640.
53. Bartlett NW, Walton RP, Edwards MR, *et al.* Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat Med* 2008; 14: 199–204.
54. Jartti T, Korppi M, Ruuskanen O. The clinical importance of rhinovirus-associated early wheezing. *Eur Respir J* 2009; 33: 706–707.
55. Kotaniemi-Syrjanen A, Laatikainen A, Waris M, *et al.* Respiratory syncytial virus infection in children hospitalized for wheezing: virus-specific studies from infancy to preschool years. *Acta Paediatr* 2005; 94: 159–165.
56. Lemanske RF Jr, Jackson DJ, Gangnon RE, *et al.* Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005; 116: 571–577.
57. Jackson DJ, Gangnon RE, Evans MD, *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178: 667–672.
58. Kusel MM, de Klerk NH, Kebadze T, *et al.* Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007; 119: 1105–1110.
59. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, *et al.* Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005; 40: 316–323.
60. Sly PD, Boner AL, Bjorksten B, *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; 372: 1100–1106.
61. Papadopoulos NG, Johnston SL. The role of viruses in the induction and progression of asthma. *Curr Allergy Asthma Rep* 2001; 1: 144–152.
62. Papadopoulos NG, Xepapadaki P, Mallia P, *et al.* Mechanisms of virus-induced asthma exacerbations: state-of-the-art. A GA2LEN and InterAirways document. *Allergy* 2007; 62: 457–470.
63. Papadopoulos NG, Bates PJ, Bardin PG, *et al.* Rhinoviruses infect the lower airways. *J Infect Dis* 2000; 181: 1875–1884.
64. Papadopoulos NG, Papi A, Meyer J, *et al.* Rhinovirus infection up-regulates eotaxin and eotaxin-2 expression in bronchial epithelial cells. *Clin Exp Allergy* 2001; 31: 1060–1066.
65. Schroth MK, Grimm E, Frindt P, *et al.* Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. *Am J Respir Cell Mol Biol* 1999; 20: 1220–1228.
66. Kelly JT, Busse WW. Host immune responses to rhinovirus: mechanisms in asthma. *J Allergy Clin Immunol* 2008; 122: 671–682.
67. Papadopoulos NG, Papi A, Psarras S, *et al.* Mechanisms of rhinovirus-induced asthma. *Paediatr Respir Rev* 2004; 5: 255–260.
68. Xatzipsalti M, Kyrana S, Tsolia M, *et al.* Rhinovirus viremia in children with respiratory infections. *Am J Respir Crit Care Med* 2005; 172: 1037–1040.
69. Kling S, Donninger H, Williams Z, *et al.* Persistence of rhinovirus RNA after asthma exacerbation in children. *Clin Exp Allergy* 2005; 35: 672–678.
70. Bossios A, Psarras S, Gourgiotis D, *et al.* Rhinovirus infection induces cytotoxicity and delays wound healing in bronchial epithelial cells. *Respir Res* 2005; 6: 114.
71. Xatzipsalti M, Psarros F, Konstantinou G, *et al.* Modulation of the epithelial inflammatory response to rhinovirus in an atopic environment. *Clin Exp Allergy* 2008; 38: 466–472.
72. Psarras S, Volonaki E, Skevaki CL, *et al.* Vascular endothelial growth factor-mediated induction of angiogenesis by human rhinoviruses. *J Allergy Clin Immunol* 2006; 117: 291–297.
73. Skevaki CL, Psarras S, Volonaki E, *et al.* Rhinovirus-induced basic fibroblast growth factor release from bronchial epithelial cells mediates airway remodelling features. Abstract No. 0416. 21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 2011. Milan, Italy.
74. Leigh R, Oyelusi W, Wiehler S, *et al.* Human rhinovirus infection enhances airway epithelial cell production of growth factors involved in airway remodeling. *J Allergy Clin Immunol* 2008; 121: 1238–1245.
75. Wark PA, Johnston SL, Bucchieri F, *et al.* Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005; 201: 937–947.

76. Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
77. Bullens DM, Decraene A, Dilissen E, *et al.* Type III IFN-lambda mRNA expression in sputum of adult and school-aged asthmatics. *Clin Exp Allergy* 2008; 38: 1459–1467.
78. Gehlhar K, Bilitewski C, Reinitz-Rademacher K, *et al.* Impaired virus-induced interferon-α2 release in adult asthmatic patients. *Clin Exp Allergy* 2006; 36: 331–337.
79. Laza-Stanca V, Message SD, Edwards MR, *et al.* The role of IL-15 deficiency in the pathogenesis of virus-induced asthma exacerbations. *PLoS pathogens* 2011; 7: e1002114.
80. Edwards MR, Johnston SL. Deficient interferon in virus-induced asthma exacerbations. *Clin Exp Allergy* 2008; 38: 1416–1418.
81. Lopez-Souza N, Favoreto S, Wong H, *et al. In vitro* susceptibility to rhinovirus infection is greater for bronchial than for nasal airway epithelial cells in human subjects. *J Allergy Clin Immunol* 2009; 123: 1384–1390.
82. Bochkov YA, Hanson KM, Keles S, *et al.* Rhinovirus-induced modulation of gene expression in bronchial epithelial cells from subjects with asthma. *Mucosal Immunol* 2010; 3: 69–80.
83. Message SD, Laza-Stanca V, Mallia P, *et al.* Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci USA* 2008; 105: 13562–13567.
84. Auais A, Adkins B, Napchan G, *et al.* Immunomodulatory effects of sensory nerves during respiratory syncytial virus infection in rats. *Am J Physiol Lung Cell Mol Physiol* 2003; 285: L105–L113.
85. Tortorolo L, Langer A, Polidori G, *et al.* Neurotrophin overexpression in lower airways of infants with respiratory syncytial virus infection. *Am J Respir Crit Care Med* 2005; 172: 233–237.
86. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005; 24: S217–S222.
87. Simpson A, Tan VY, Winn J, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010; 181: 1200–1206.
88. Illi S, von Mutius E, Lau S, *et al.* Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; 368: 763–770.
89. Hollams EM, Hales BJ, Bachert C, *et al.* Th2-associated immunity to bacteria in teenagers and susceptibility to asthma. *Eur Respir J* 2010; 36: 509–516.
90. Green RM, Custovic A, Sanderson G, *et al.* Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002; 324: 763.
91. Lopez-Souza N, Dolganov G, Dubin R, *et al.* Resistance of differentiated human airway epithelium to infection by rhinovirus. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L373–L381.
92. Jakiela B, Brockman-Schneider R, Amineva S, *et al.* Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. *Am J Respir Cell Mol Biol* 2008; 38: 517–523.
93. Bossios A, Gourgiotis D, Skevaki CL, *et al.* Rhinovirus infection and house dust mite exposure synergize in inducing bronchial epithelial cell interleukin-8 release. *Clin Exp Allergy* 2008; 38: 1615–1626.
94. Friedlander SL, Busse WW. The role of rhinovirus in asthma exacerbations. *J Allergy Clin Immunol* 2005; 116: 267–273.
95. Wenzel S, Wilbraham D, Fuller R, *et al.* Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007; 370: 1422–1431.
96. Subrata LS, Bizzintino J, Mamessier E, *et al.* Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. *J Immunol* 2009; 183: 2793–2800.
97. Robays LJ, Maes T, Lebecque S, *et al.* Chemokine receptor CCR2 but not CCR5 or CCR6 mediates the increase in pulmonary dendritic cells during allergic airway inflammation. *J Immunol* 2007; 178: 5305–5311.
98. Kato A, Favoreto S Jr, Avila PC, *et al.* TLR3- and Th2 cytokine-dependent production of thymic stromal lymphopoietin in human airway epithelial cells. *J Immunol* 2007; 179: 1080–1087.
99. Holt PG, Strickland DH. Interactions between innate and adaptive immunity in asthma pathogenesis: new perspectives from studies on acute exacerbations. *J Allergy Clin Immunol* 2010; 125: 963–972.
100. Holt PG, Sly PD. Interaction between adaptive and innate immune pathways in the pathogenesis of atopic asthma: operation of a lung/bone marrow axis. *Chest* 139: 1165–1171.
101. Turato G, Barbato A, Baraldo S, *et al.* Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. *Am J Respir Crit Care Med* 2008; 178: 476–482.
102. Biscione GL, Corne J, Chauhan AJ, *et al.* Increased frequency of detection of *Chlamydophila pneumoniae* in asthma. *Eur Respir J* 2004; 24: 745–749.
103. Freymuth F, Vabret A, Brouard J, *et al.* Detection of viral, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in exacerbations of asthma in children. *J Clin Virol* 1999; 13: 131–139.
104. Allegra L, Blasi F, Centanni S, *et al.* Acute exacerbations of asthma in adults: role of *Chlamydia pneumoniae* infection. *Eur Respir J* 1994; 7: 2165–2168.
105. Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA* 1991; 266: 225–230.
106. Hahn DL, Golubjatnikov R. Asthma and chlamydial infection: a case series. *J Fam Pract* 1994; 38: 589–595.

107. Betsou F, Sueur JM, Orfila J. Anti-*Chlamydia pneumoniae* heat shock protein 10 antibodies in asthmatic adults. *FEMS Immunol Med Microbiol* 2003; 35: 107–111.
108. Cook PJ, Davies P, Tunnicliffe W, *et al. Chlamydia pneumoniae* and asthma. *Thorax* 1998; 53: 254–259.
109. Cunningham AF, Johnston SL, Julious SA, *et al.* Chronic *Chlamydia pneumoniae* infection and asthma exacerbations in children. *Eur Respir J* 1998; 11: 345–349.
110. Emre U, Roblin PM, Gelling M, *et al.* The association of *Chlamydia pneumoniae* infection and reactive airway disease in children. *Arch Pediatr Adolesc Med* 1994; 148: 727–732.
111. Esposito S, Droghetti R, Bosis S, *et al.* Cytokine secretion in children with acute *Mycoplasma pneumoniae* infection and wheeze. *Pediatr Pulmonol* 2002; 34: 122–127.
112. Meloni F, Paschetto E, Mangiarotti P, *et al.* Acute *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infections in community-acquired pneumonia and exacerbations of COPD or asthma: therapeutic considerations. *J Chemother* 2004; 16: 70–76.
113. Miyashita N, Kubota Y, Nakajima M, *et al. Chlamydia pneumoniae* and exacerbations of asthma in adults. *Ann Allergy Asthma Immunol* 1998; 80: 405–409.
114. Thumerelle C, Deschildre A, Bouquillon C, *et al.* Role of viruses and atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region (France). *Pediatr Pulmonol* 2003; 35: 75–82.
115. Gern JE, Lemanske RF Jr. Infectious triggers of pediatric asthma. *Pediatr Clin North Am* 2003; 50: 555–575.
116. Gendrel D, Raymond J, Moulin F, *et al.* Etiology and response to antibiotic therapy of community-acquired pneumonia in French children. *Eur J Clin Microbiol Infect Dis* 1997; 16: 388–391.
117. Principi N, Esposito S, Blasi F, *et al.* Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired lower respiratory tract infections. *Clin Infect Dis* 2001; 32: 1281–1289.
118. Principi N, Esposito S. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* cause lower respiratory tract disease in paediatric patients. *Curr Opin Infect Dis* 2002; 15: 295–300.
119. ten Brinke A, van Dissel JT, Sterk PJ, *et al.* Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of *Chlamydia pneumoniae* infection. *J Allergy Clin Immunol* 2001; 107: 449–454.
120. Hardy RD, Jafri HS, Olsen K, *et al. Mycoplasma pneumoniae* induces chronic respiratory infection, airway hyperreactivity, and pulmonary inflammation: a murine model of infection-associated chronic reactive airway disease. *Infect Immun* 2002; 70: 649–654.
121. Pasternack R, Huhtala H, Karjalainen J. *Chlamydophila* (*Chlamydia*) *pneumoniae* serology and asthma in adults: a longitudinal analysis. *J Allergy Clin Immunol* 2005; 116: 1123–1128.
122. Schmidt SM, Muller CE, Wiersbitzky SK. Inverse association between *Chlamydia pneumoniae* respiratory tract infection and initiation of asthma or allergic rhinitis in children. *Pediatr Allergy Immunol* 2005; 16: 137–144.
123. Bisgaard H, Hermansen MN, Buchvald F, *et al.* Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007; 357: 1487–1495.
124. Bisgaard H, Hermansen MN, Bonnelykke K, *et al.* Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ* 2010; 341: c4978.

Chapter 11

Role of allergen exposure on the development of asthma in childhood

Susanne Lau

SUMMARY: Asthma is one of the most frequent chronic diseases and various phenotypes in infancy and childhood have been described. Approximately two-thirds of schoolchildren are allergic to inhalant allergens. In particular, mite allergy and pet allergy are associated with chronic allergic airway disease, and continuous exposure may cause a decline in lung function in early life. However, in terms of a dose–response relationship between exposure and sensitisation and exposure and asthma the literature is controversial. Therefore, the structure of preventive measures may vary for different phenotypes in different areas of the world.

KEYWORDS: Allergen exposure, allergen sensitisation, asthma phenotypes

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Asthma is a frequent chronic disease in childhood. Recurrent wheeze during the first 3 years of life is associated with viral infections such as respiratory syncytial virus (RSV), rhinovirus, parainfluenza, bocavirus, picornavirus, human metapneumovirus, and many others. RSV in particular is associated with bronchial hyperresponsiveness (BHR) and consecutive obstructive airway disease that may last for many years after the first episode of lower airway infection [1]. Parents with asthma are the genetic risk factor for asthma in their offspring, with parental asthma increasing the risk three-fold [2]; however, conflicting data have been reported on the significance of allergen exposure, especially indoor allergens such as furry pets and house dust mites.

Sensitisation and allergen exposure: link to childhood asthma

Most of the published studies to date have failed to prove a direct relationship between allergen exposure and the development of allergic asthma; however, sensitisation to indoor allergens is clearly related to allergic asthma [3–6]. Furthermore, continuous exposure to indoor allergens is a risk factor for a decline in lung function in already sensitised schoolchildren (fig. 1) [9] and the severity of paediatric asthma [10]. In children with asthma aged 13 years, sensitisation to indoor allergens increases the risk of developing asthma in puberty three-fold for those with wheeze

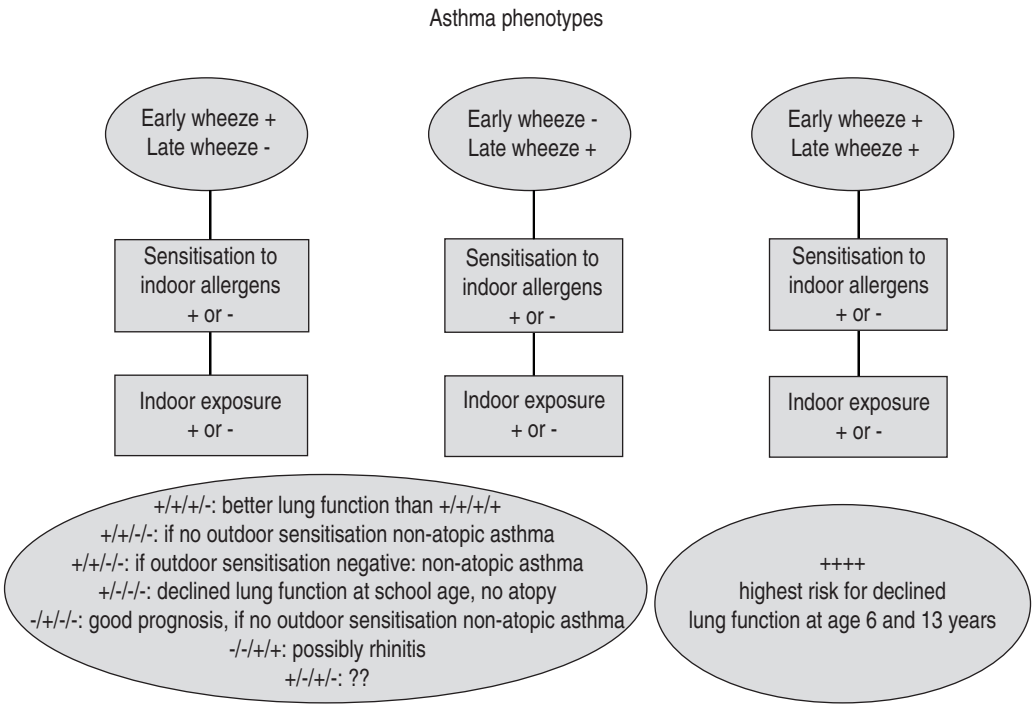
Asthma phenotypes
Early wheeze +
Late wheeze -
Early wheeze -
Late wheeze +
Early wheeze +
Late wheeze +
Sensitisation to indoor allergens + or -
Sensitisation to indoor allergens + or -
Sensitisation to indoor allergens + or -
Indoor exposure + or -
Indoor exposure + or -
Indoor exposure + or -
+/+/+/-: better lung function than +/+/+/+
+/+/-/-: if no outdoor sensitisation non-atopic asthma
+/+/-/-: if outdoor sensitisation negative: non-atopic asthma
+/-/-/-: declined lung function at school age, no atopy
-/+/-/-: good prognosis, if no outdoor sensitisation non-atopic asthma
-/-/+/+: possibly rhinitis
+/-/+/-: ??
++++
highest risk for declined lung function at age 6 and 13 years

Figure 1. Different asthma phenotypes and prognosis. Data taken from [2, 6, 7, 8].

before 3 years of age and seven-fold for those who start wheezing after their third birthday (table 1) [2]. For early childhood (preschool age), sensitisation to *Alternaria*, cat, house dust mites and grass pollen appear to be strongly linked to an asthmatic phenotype [11].

There is evidence indicating that immunoglobulin (Ig)E antibody responses do not reflect a single phenotype of atopy, but several different atopic vulnerabilities that differ in their relationship with asthma presence and severity [7]. In a five-class model indicating a latent structure, children with multiple early sensitisations reported the worst lung function at 8 years of age compared to those without atopy.

In terms of a dose–response relationship between allergen exposure and airway disease, most reports are on house dust mites and pet exposure; however, the literature is quite controversial on the significance of pet exposure. There may be differences in areas with a high prevalence *versus* areas with a low prevalence of pet or cat keeping [12]. In Germany, for instance, exposure seems to be much lower than in the UK or the USA. Sensitisation can occur *via* inhalation but it is reported in infants with atopic dermatitis, thus, because of an impaired barrier function sensitisation can occur *via* the skin.

Pet allergens

Cat and dog allergens can be found in homes and in public places such as schools, *etc.* [13, 14]. Allergic sensitisation can occur in high- and low-exposure areas; therefore, allergen reduction with air-cleaners appears not to be very effective in terms of primary and secondary prevention [15, 16]. However, exposure in

Table 1. Predictive value of early-life factors to predict wheezing at age 11–13 years

Wheeze <3 years PLUS High indoor allergen exposure: house dust mites and cats PLUS Sensitisation to house dust mites and cats <3 years	→	Specificity 99.7% Sensitivity 9.3% PPV 83.3% NPV 87.5%

PPV: positive predictive value; NPV: negative predictive value. Data taken from [2].

sensitised asthmatic individuals worsens symptoms [17]. Results from a Norwegian study and the European Community Respiratory Health Survey (ECRHS) indicate that cat exposure in early life is a risk factor for later onset allergy and asthma [12, 18], while other studies suggest a protective effect of early-life pet exposure [19, 20]. As allergic children often have allergic parents causing avoidance behaviour towards pets, reverse causation must always be taken into account. Sensitisation was found to be strongly related to asthma in German and British longitudinal studies. While 50% of mite-sensitised children showed asthmatic symptoms at 4 years of age, 44% of cat-sensitised children were asthmatic [5, 11]. Can f 1, a major dog allergen, appears to be less allergenic than cat allergen due to the similarity of the lipocalin protein family to human serum proteins. Some authors suggest that exposure to dogs is associated with increased exposure to bacterial compounds such as endotoxin, thus modulating the immune response and decreasing the risk for allergy and asthma [21, 22]. In a Canadian study, dog ownership during the first year of life was associated with an increased risk of asthma at age 7 years but was not associated with specific sensitisation [23]. Nevertheless, a recent meta-analysis on pet exposure in European birth cohort studies showed no clear association between the development of asthma and pet exposure; therefore, avoidance can only be recommended as a therapeutic approach (K.C. Lødrup Carlsen, Dept of Paediatrics, Oslo University Hospital, Oslo, Norway; personal communication).

House dust mite

House dust mite exposure is dependent on the regional climate and on the microclimate in homes. *Dermatophagoides* spp. require a higher indoor humidity (more than 70% relative humidity) and a constant temperature (optimum approximately 24°C). Usually, these conditions can be found in mattresses. However, in dry and hot or colder areas, such as deserts or the northern European countries (*e.g.* Sweden and Norway), exposure to house dust mites is rarely reported to be a major problem. In the German Multicentre Allergy Study (MAS), sensitisation to house dust mites in early life was a risk factor for school-age asthma [5], exposure in the first year of life was not directly related to later onset asthma but to specific sensitisation. Similar results were reported from a Canadian study [23]. In another birth cohort study from Boston (MA, USA) in infancy, exposure to more than 10 μg of mite allergen per gram of dust was related to the development of childhood asthma at age 7 years; in particular, the risk for late-onset asthma increased five-fold. High exposure to endotoxin decreased the risk for asthma [24].

However, primary prevention procedures reducing domestic mite-allergen exposure have unfortunately not achieved decreased sensitisation rates. In contrast, while 3-year-old children were found to have less airway resistance, they showed higher sensitisation rates than the control group [16]. However, mite-allergen reduction as a tertiary approach can effectively reduce symptoms and BHR [25–27], although a meta-analysis was not in agreement with these findings [28]. When analysing effect sizes only studies that successfully achieved allergen reduction with similar methods can be included, applying mite avoidance measures to a clearly defined mite-allergic population [29–31]. The Childhood Asthma Management Program in the USA reported allergen sensitisation and exposure to indoor allergens to be risk factors decreasing the likelihood of remitting asthma in adolescence [32].

Cockroach

Cockroach allergen exposure does not play a major role in northern European countries, such as Germany, Austria and Switzerland. It is a common problem in many areas of the USA, South America and Mediterranean countries. Exposure and sensitisation are associated with inner-city asthma and lower social status [33, 34]. In the USA, 60–80% of the inner-city asthma population is often sensitised to cockroach allergens [35]. The poorer outcome and increased asthma-related healthcare utilisation (emergency rooms) in inner-city children with asthma and

cockroach sensitisation may also be linked to social status, exposure to other risk factors such as fast food, obesity, tobacco smoke exposure, *etc.*, and poorer access to pharmacotherapy (inhaled corticosteroids (ICS)).

Mould

At present there is not much direct evidence on the association between moulds and asthma. Indoor moulds reflect bad housing conditions, such as poor insulation and problems with humidity. Sensitisation to moulds (*Alternaria* and *Penicillium*) increases the risk of asthma [36–38]. However, as reported in a recent study, exposure to β(1,2)-glucans from moulds seems to be beneficial in preventing allergic sensitisation [38].

Discussion

Asthma is a complex disease with different phenotypes and underlying pathophysiology. In the PRACTALL (PRACtical ALLergy) consensus experts tried to define five different endotypes [40]. Therefore, allergen exposure may play a different role in different phenotypes. If the child is allergic, allergen exposure increases airway inflammation and may be associated with the risk of hospital admission, especially if sensitisation had already occurred in early life [41]. Allergen sensitisation and high-level exposure to sensitising allergen and respiratory virus infection synergistically increases the risk of acute exacerbation among adults and among children [42, 43]. However, there are also children with asthma without any sensitisation. For this group, infections, physical exercise and other triggers such as cold air play a major role.

For the prevention of asthma, in terms of pollen allergy and hay fever, early immunotherapy has to be taken into consideration [44]. Unfortunately, there are no studies showing that immunotherapy in children with allergic rhinitis and mite allergy can be preventative for asthma. In mite-allergic asthmatic children, avoidance of allergens can modulate BHR [26]. Different phenotypes require different therapeutic and preventive measures. Thus, avoidance of indoor allergens is appropriate in children with early or late indoor sensitisation to mite or pet allergens in order to avoid continuous exposure, bronchial inflammation and decline of lung function. Attempts to predict the natural course of childhood asthma, *i.e.* remission, relapse and persistence, show that prediction is only possible for certain subgroups with a defined risk factor. In the Isle of Wight Birth Cohort Study (UK), four risk factors were identified: 1) family history of asthma, 2) recurrent chest infections in infancy, 3) absence of nasal symptoms at age 1 year, and 4) atopic sensitisation at age 4 years. MATRICARDI *et al.* [8] and SCOTT *et al.* [45] used this exact algorithm in the German MAS cohort and found a positive predictive value of 0.65 (95% CI 0.44–0.82) with a cut-off value of 3 in the risk score strata. Using an algorithm based on early wheezing, sensitisation to mites and elevated allergen exposure, a better prediction for asthma at age 13 years in the German MAS could be achieved (positive predictive value 0.83) [2, 8].

Conclusion

In conclusion: 1) allergen exposure is important for the development of allergic sensitisation and allergic asthma in approximately 60–75% of asthmatic schoolchildren; 2) sensitisation to indoor allergens can occur very early in life, and possibly *via* the skin in infants with atopic dermatitis; 3) avoidance of indoor allergen may be useful in order to prevent deterioration of lung function in sensitised individuals; 4) different phenotypes of asthma require different therapeutic and preventive measures; and 5) primary prevention of allergic asthma is not possible at the moment.

Statement of Interest

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References

1. Mohapatra SS, Boyapalle S. Epidemiologic, experimental and clinical links between respiratory syncytial virus infection and asthma. *Clin Microbiol Rev* 2008; 21: 495–504.
2. Matricardi P, Illi S, Grueber C, *et al.* Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008: 32; 585–592.
3. Ahluwalia SK, Matsui EC. The indoor environment and its effect on childhood asthma. *Curr Opin Allergy Clin Immunol* 2011; 11: 137–143.
4. Arshad SA, Tariq SM, Matthews S, *et al.* Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population cohort study. *Pediatrics* 2001; 108: E33.
5. Lau S, Illi S, Sommerfeld C, *et al.* Early exposure to house dust mite and cat allergens and the development of childhood asthma. *Lancet* 2000; 356: 1392–1397.
6. Sqillace SP, Sporik RB, Rakes G, *et al.* Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia: multiple regression analysis of a population-based study. *Am J Respir Crit Care Med* 1997; 156: 1760–1764.
7. Simpson A, Tan VY, Winn J, *et al.* Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am Respir Crit Care Med* 2011; 181: 1200–1206.
8. Matricardi PM, Illi S, Keil T, *et al.* Predicting persistence of wheezing: one algorithm does not fit all. *Eur Respir J* 2010; 35: 701–703.
9. Illi S, von Mutius E, Lau S, *et al.* Perennial allergen sensitization early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; 368: 763–770.
10. Gent JF, Belanger K, Triche EW, *et al.* Association of pediatric asthma severity with exposure to common household dust allergens. *Environ Res* 2009; 109: 768–774.
11. Arshad SH. Does exposure to indoor allergens contribute to the development of asthma and allergy? *Curr Allergy Asthma Rep* 2010; 10: 49–55.
12. Svanes C, Heinrich J, Jarvis D, *et al.* Pet-keeping in childhood and adult asthma and hay fever: European Community Respiratory Health Survey. *J Allergy Clin Immunol* 2003; 112: 289–300.
13. Almqvist C, Larrson PH, Egmar AC, *et al.* School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *J Allergy Clin Immunol* 1999; 103: 1012–1017.
14. Custovic A, Fletcher A, Pickering CA, *et al.* Domestic allergens in public places III: house dust mite, cat, dog, and cockroach allergens in British hospitals. *Clin Exp Allergy* 1998; 28: 53–59.
15. Sulser C, Schulz G, Wagner P, *et al.* Can the use of HEPA cleaners in homes of asthmatic children and adolescents sensitised to cat and dog allergens decrease bronchial hyperresponsiveness and allergen contents in solid dust? *Int Arch Allergy Immunol* 2009; 148: 23–30.
16. Woodcock A, Lowe LA, Murray CS, *et al.* Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; 122: 662–668.
17. Almqvist C, Wickman M, Perfetti L, *et al.* Worsening of asthma in children allergic to cats, after indirect exposure to cats at school. *Am J Respir Crit Care Med* 2001; 163: 694–698.
18. Bertelsen RJ, Lodrup Carlsen KC, Carlsen K-H, *et al.* Childhood asthma and early life exposure to indoor allergens, endotoxin, and β(1,3)-glucans. *Clin Exp Allergy* 2010; 40: 307–316.
19. Kerkhof M, Wijga AH, Brunekreef B, *et al.* Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy* 2009; 64: 1202–1208.
20. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first years of life and risk of allergic sensitization at 6 to 7 years of age. *J Am Med Assoc* 2002; 288: 963–972.
21. Campo P, Kalra HK, Levin L, *et al.* Influence of dog owenership and high endotoxin on wheezing and atopy during infancy. *J Allergy Clin Immunol* 2006; 118: 1271–1278.
22. Hugg TT, Jaakkola MS, Ruotsalainen R, *et al.* Exposure to animals and the risk of allergic asthma: a population-based cross-sectional study in Finish and Russian children. *Environ Health* 2008; 7: 28.
23. Carlsten C, Dimich-Ward H, Becker AB, *et al.* Indoor allergen expsoure, sensitization, and development of asthma in a high-risk birth cohort. *Pediatr Allergy Immunol* 2010; 21: e740–e746.
24. Celedon JC, Milton DK, Ramsey CD, *et al.* Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007; 120: 144–149.
25. Carswell F, Birmingham K, Oliver J, *et al.* The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children: a double-blind controlled trial. *Clin Exp Allergy* 1996; 26: 386–396.
26. Ehnert B, Lau-Schadendorf S, Weber A, *et al.* Reducing domestic exposure of dust mite allergen reduces bronchial hyperreactivity in sensitive asthmatic children. *J Allergy Clin Immunol* 1992; 90: 135–138.
27. Halken S, Host A, Niklassen U, *et al.* Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003; 111: 169–176.
28. Gotzsche PC, Johannsen HK. House dust mite control measures for asthma: systematic review. *Allergy* 2008; 63: 646–659.
29. Kopp MV, Niggemann B, Forster J. House dust mite allergy: complete removal of the provoking allergen is a primary therapeutic approach. *Allergy* 2009; 64: 187–188.
30. Kopp MV, Niggemann B, Forster J. House dust mite allergy: complete removal of the provoking allergen is a primary therapeutic approach. *Allergy* 2009; 64: 1402–1403.

31. Platts-Mills TA. Allergen avoidance in the treatment of asthma: problems with meta-analyses. *J Allergy Clin Immunol* 2008; 122: 694–696.
32. Covar RA, Strunk R, Zeiger R, *et al.* Predictors of remitting, periodic, and persistent childhood asthma. *J Allergy Clin Immunol* 2010; 125: 359–366.
33. Donohue KM, Al-Alem U, Perzanowski MS, *et al.* Anticockroach and antimouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. *J Allergy Clin Immunol* 2008; 122: 914–920.
34. Wang J, Visness CM, Calatroni A, *et al.* Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. *Clin Exp Allergy* 2009; 39: 1381–1389.
35. Gruchalla RS, Pongracic J, Plaut M, *et al.* Inner City Asthma Study: relationship among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol* 2005; 115: 476–485.
36. Bush RK, Prochnau JJ. *Alternaria*-induced asthma. *J Allergy Clin Immunol* 2004; 113: 227–234.
37. Downs SH, Mitakikis TZ, Marks GB, *et al.* Clinical importance of *Alternaria* exposure in children. *Am J Respir Crit Care Med* 2001; 164: 445–449.
38. Pongracic JA, O'Connor GT, Muilenberg ML, *et al.* Differntial effects of outdoor *versus* indoor fungal spores on asthma morbidity in inner-city children. *J Allergy Clin Immunol* 2010; 126: 593–599.
39. Tischer C, Gehring U, Chen CM, *et al.* Respiratory health in children, and indoor exposure to (1,3)-β-D-glucan, EPS mould components and endotoxin. *Eur Respir J* 2011; 37: 1050–1059.
40. Lötvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127: 355–360.
41. Custovic A, Simpson A, Bardin PG, *et al.* Allergy is an important factor in asthma exacerbation: a pro/con debate. *Respirology* 2010; 15: 1021–1027.
42. Green RM, Custovic A, Sanderson G, *et al.* Synergism between allergens and viruses and risk of hospital admission with asthma. *BMJ* 2002; 324: 763.
43. Murray CS, Poletti G, Kebadze T, *et al.* Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006; 61: 376–382.
44. Jacobsen L, Niggemann B, Dreborg S, *et al.* Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62: 943–948.
45. Scott M, Kurukulaaratchy RJ, Raza A, *et al.* Understanding the nature and outcome of childhood wheezing. *Eur Respir J* 2009; 33: 700–701.

Chapter 12

Indoor and outdoor air pollution and the development of asthma

Jonathan Grigg

SUMMARY: Over the last decade there have been significant advances in our understanding of the health effects of air pollution in children. Linking data from large prospective cohort studies to locally generated air pollution clearly demonstrates that exposure to both traffic emissions and indoor second-hand smoke are important risk factors for the development of preschool wheeze and school-age asthma. Uncertainties still remain, especially about the size of this association, and the individual components responsible for driving increased vulnerability to asthma. Improvements in modelling and new ways of thinking about exposure, for example combining second-hand smoke with traffic emissions into a single exposure variable, may help policy makers take the decisions necessary to reduce the long-term health burden of indoor and outdoor pollution in children.

KEYWORDS: Air pollution, asthma, children, second-hand tobacco smoke

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There is good evidence from both cross-sectional and panel studies that exposure to air pollution is associated with increased wheeze in asthmatic children. More controversial is whether exposure to air pollution increases the risk of developing asthma. The aim of this chapter is to review: 1) the key pollutants that European children are exposed to both indoors and outdoors; 2) the type of studies needed to address the question of asthma development; and 3) the evidence for an association between air pollution and new-onset asthma. This chapter focuses on combustion-derived pollutants. The association between new-onset asthma and exposure to other environmental threats such as household chemicals, formaldehyde, allergens and damp will not be considered.

Outdoor pollution

Exposure of children to outdoor air pollution is the sum of the background level of pollution and locally generated emissions. Children within cities are exposed to the same background level of pollutants. Background pollution is therefore not useful when studying a cohort recruited within the same city/area, unless there is an extensive network of monitoring stations. However, because

the background level varies from day to day it can be used in panel studies where the daily variation in background pollution is linked to the daily variation in lung function/symptoms. Locally generated pollution, in contrast, is the major driver of the variation in exposure within cites. Both background and locally generated pollution is composed of particulate matter (PM) and gases. PM is defined by the way it is measured for regulatory purposes, either as PM with a 50% cut-off aerodynamic diameter of 10 μm (PM10) or as PM with an aerodynamic diameter of <2.5 μm (PM2.5). Measurement of PM is normally performed by the tapered element oscillating microbalance (TEOM), a device that constantly aspirates ambient air, diverts PM <10 μm (or PM <2.5 μm) into the machine and deposits PM onto a filter. The weight of the filter, when combined with the inlet gas flow rate, generates the PM concentration ($\mu g \cdot m^{-3}$). PM consists of: 1) primary particles emitted directly from combustion sources, and 2) secondary particles produced by reactions between other pollutants in the air. Primary PM tends to be dominated by soot, *i.e.* aggregates of nanoparticles with an elemental black carbon core, whereas secondary PM includes non-carbonaceous particles such as nitrates and sulfates. The main sources of outdoor PM are emissions from motor vehicles (18%), industry (36%) and long distance transport of secondary particles into urban areas [1]. The soot component of combustion PM is best represented by the "black carbon" metric. Black carbon is measured by drawing air through a filter and measuring the filter's blackness by reflecting light off the spot. Black carbon is currently not used for regulatory purposes.

Nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) are the main outdoor pollutant gases. NO_2 is formed by oxidation of nitric oxide by either ozone or oxygen emitted from vehicle exhausts (30% of the source of NO_2 in urban areas), power stations and industry (46%) [1]. SO_2, in contrast, is not a major fossil fuel emission component, since it is generated by burning high-sulfur containing coal. SO_2 is a limited issue in European cities because power stations are normally located outside urban areas and burn low-sulfur coal. Ozone is formed when sunlight in the lower atmosphere acts on oxides of nitrogen and volatile organic compounds, *i.e.* it is not directly emitted from combustion sources. The atmospheric chemistry of ozone is complex. Nitrogen oxides (NOx) not only contribute to the formation of ozone but also to its removal since ozone reacts with nitrogen oxide to produce NO_2. Thus, reducing the level of NOx may perversely increase ambient ozone [1].

Air quality standards are in place in the European Union (EU) for PM10, NO_2, O_3 and SO_2. Unfortunately, most European cities currently fail to meet current standards. For example, the EU has recently launched an infringement proceeding against the UK for failing to comply with the air quality standard for PM10. Indeed, a recent report from the UK parliament concluded that "the UK should be ashamed of its poor air quality" and "more comprehensive cost benefit analysis should drive both changes in policy and better implementation of existing policy" [2]. There are not only regulatory levels for air pollutants but also expert panels produce specific advice on what actions to take during high pollution days. The most recent recommendation (air quality index) for the UK population is described in table 1. To date, EU standards and air quality indexes are based on studies of the short-term effects of air pollution. Long-term effects such as decreased lung growth, or the development of disease such as asthma have not been integrated into the standard setting process.

Indoor pollution

Indoor air pollution consists of pollutants generated both inside the home and pollution entering the home from the outside. ESPLUGUES *et al.* [3] used passive samplers to measure indoor and outdoor NO_2 levels in and around the homes of 352 children. Indoor levels of NO_2 were lower indoors than outdoor (18 $\mu g \cdot m^{-3}$ *versus* 26 $\mu g \cdot m^{-3}$). Outdoor NO_2 was higher in homes located in urban areas, especially those located on streets with a high frequency of vehicle traffic. Gas cooking and butane water heating were also independent determinants of indoor NO_2. There was a significant influence effect of outdoor NO_2 on indoor NO_2, accounting for 60% of the variability

Table 1. The recommended air quality index for the UK

Pollutant	Averaging period	Low $\mu g \cdot m^{-3}$	Moderate $\mu g \cdot m^{-3}$	High $\mu g \cdot m^{-3}$	Very high $\mu g \cdot m^{-3}$
PM_{10}	24-hour mean	0–50	51–75	76–75	⩾101
$PM_{2.5}$	24-hour mean	0–35	36–53	54–70	⩾71
Sulfur dioxide	15-minute mean	0–265	266–531	532–1063	⩾1064
Nitrogen dioxide	Running 8-hour mean	0–200	201–400	401–600	⩾601
Ozone	1-hour mean	0–80	81–160	161–240	⩾241
Carbon monoxide	Recommend removal from index				

PM_{10}: particles with a 50% cut-off aerodynamic diameter of 10 μm; $PM_{2.5}$: particles with an aerodynamic diameter of <2.5 μm. Each exposure band (low to very high) is accompanied by advice on action. At ''very high'' pollutant levels, at-risk individuals are advised to avoid strenuous exercise and asthmatics are advised that they may need to use salbutamol more often. Reproduced and modified from [1] with permission from the publisher.

of indoor levels. An effect of local traffic on indoor pollution was confirmed by BÉRUBÉ *et al.* [4] who measured indoor and outdoor PM_{10} levels in UK homes, and reported a significant correlation between the indoor PM_{10} and the vehicle volume that passed each home. In a more detailed investigation of indoor-generated sources of PM performed in homes in Boston (MA, USA), PM was found to be increased by cooking, cleaning and the movement of people. $PM_{2.5}$ was increased by oven cooking, toasting and barbecuing, whereas $PM_{2.5}$ to PM_{10} were increased by sautéing, cleaning and the movement of people. Smoking is also an important source of indoor PM. BÉRUBÉ *et al.* [4] found that the mean concentration of PM in homes with smokers was 15 $\mu g \cdot m^{-3}$ higher than nonsmoking homes. The additional PM_{10} burden from second-hand smoke is associated with the number of smokers and may be up to 44 $\mu g \cdot m^{-3}$.

In summary, the major exposures of young children to combustion-derived pollutants outdoors are PM, NO_2 from traffic and ozone on sunny days. Indoor exposures are from outdoor traffic-derived PM and NO_2 entering the home, in addition to NO_2 from indoor cooking and PM from second-hand smoke. One of the most confusing aspects of air pollution science is the lack of clarity on which components are directly responsible for health effects and which components are merely bystanders. However, there is a consensus that PM is detrimental to human health with robust epidemiological data backed up by animal and cell studies. For example, of the triggers for myocardial infarction, the population attributable fraction due to exposure to PM (per 30 $\mu g \cdot m^{-3}$ difference) is 7.4. This level is higher than many other variables such as exertion or even cocaine use [5]. Even though PM *per se* is likely to be a cause of lung and cardiovascular disease, it remains unclear what inhalable size fraction of PM and what component of PM is responsible for health effects. The evidence for a causal role for NO_2 is debatable. Indeed, some researchers argue that many of the reported associations between NO_2 and health effects are in fact due to PM. There is, however, consensus that outdoor NO_2 is a good marker of traffic-derived emissions. Since ozone and second-hand tobacco smoke are not highly correlated with outdoor PM or NO_2, interpretation of associations between these pollutants and health effects is less controversial.

Assessing exposure

To answer the question of whether air pollution causes asthma requires linking longitudinal symptom data to long-term assessment of exposure. Assessing asthma development is not straightforward since the concept of asthma as a single disease has undergone revision. For example, a *Lancet* editorial stated ''with every new piece of the puzzle, the notion of asthma as one unifying disease concept is disappearing further into the realm of historical oversimplification'' [6]. Studies of preschool children clearly show that most wheeze in this age group is not associated with atopy and usually resolves by 5 years of age (preschool viral wheeze) [7]. In school-age

children, the current view remains that most chronic wheeze is due to chronic eosinophilic airway inflammation. However, in some adults asthma symptoms are associated only with neutrophilic airway inflammation (neutrophilic asthma). The question of asthma phenotypes is not academic as air pollution may only be associated with the development of specific phenotypes. It is therefore important that epidemiological studies carefully define symptoms patterns and associated risk factors, such as atopy. In general, wheeze reported by parents of preschool children (especially those below 3 years of age) is likely be the transient preschool viral wheeze phenotype, *i.e.* wheeze occurring mainly with colds with no underlying chronic airway inflammation between attacks. In contrast, ''wheeze in last 12 months'', or ''doctor-diagnosed asthma'', in school-age children is likely to reflect classical atopic asthma phenotype with a tendency for chronic eosinophilic airway inflammation.

The gold standard for assessing exposure of children to air pollutants is personal measurement, followed by direct measurement in the home. Short-term monitoring of personal/home exposure to PM is feasible, but PM monitors are currently too expensive, loud and bulky to be used over the long term. In contrast, medium to long-term personal/home measurement of NO_2 is feasible using passive diffusion tubes or personal badges. For example, SUNYER *et al.* [8] assessed average 2 week indoor NO_2 in 1,611 infants and found no association between indoor NO_2 and respiratory infections in the first year of life. Fixed air pollution monitors for outdoor pollutants are sited in most European cities and are used to assess compliance with EU regulations and provide pollution warnings. Fixed monitoring is best suited to assessing long-term exposure of children to background urban pollution in ''between city'' studies. For example, the 12 Community Southern California study assigned the same monitored background exposure to PM to adolescent children living within each community and differences in background PM between communities were found to be associated with reduced growth of lung function [9]. As discussed previously, the variation in exposure of children within cities to PM and NO_2 is driven by proximity to traffic. Since children spend a large proportion of time at home, and there is a band of high pollution up to 150 m from heavily used roads, the distance of the home to the nearest main road is a valid way of assessing long-term exposure in large numbers of children. In some studies, the home road distance is refined by adjusting for the mix of traffic on the road using survey data, and adding in real-time data such as wind direction. This type of dispersion modelling gives a metrological estimate of the concentration of locally generated pollutants at the home address. Additional complexity is achieved by adding in actual measured pollutant levels from networks of within-city pollution monitors. In a secondary analysis of the 12 Community Southern California study, researchers assessed exposure to local air pollution. Children who lived within 500 m of a heavily used road had deficits in 8-year growth of forced expiratory volume in 1 second (FEV_1) and maximum mid-expiratory flow rate compared with children who lived at least 1,500 m away from a heavily used road [10], *i.e.* both local and regional (background) air pollution have independent adverse effects on lung function growth. In contrast to traffic-derived pollution, exposure to cigarette smoke does not need to be measured directly since parents are the main source and they can be asked about their smoking behaviour. A single urinary cotinine of validating parent-reported exposure to second-hand smoke is only accurate for the previous 3 days' exposure. Long-term accurate validation of second-hand smoke exposure requires repeated urine samples [11].

Traffic pollution and new-onset asthma

To address the question of whether air pollution causes childhood asthma, studies must prospectively record incident symptoms and estimate long-term (ideally whole-life) exposure to air pollution. Valid, albeit imprecise, methods for estimating long-term exposure in children are to use proximity to source (*e.g.* distance of the home to the nearest main road) or to directly measure a marker of traffic-derived pollution (*e.g.* NO_2).

Several cross-sectional studies have assessed incident symptoms in the first years of life. Since newborns are asymptomatic, wheeze prevalence in the early years reflects new-onset wheeze. In the

Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study in the Netherlands, BRAUER *et al.* [12] used an air pollution model that combined actual air pollution measurements with distance from road data, in a birth cohort of 4,000 infants surveyed up to 4 years of age. As one would expect, the correlation between PM and NO_2 was high (>0.90). At 4 years of age, 4% of children had doctor-diagnosed asthma and 12% had parent-reported wheeze. Linking symptoms with exposure, there was an association between an interquartile increase in either $PM_{2.5}$, or black carbon, and wheeze (OR 1.2, 95% CI 1.0–1.4) and doctor-diagnosed asthma (OR 1.3, 95% CI 1.0–1.7). In the same age group, CLARK *et al.* [13] assessed incident (*i.e.* new-onset) asthma in 37,000 children born in British Colombia between 1999 and 2000. First year life pollution exposure was assessed using an air pollution model that extrapolated exposure from a network of fixed monitoring stations. All the traffic-derived pollutants (black carbon, PM_{10} and NO_2) when entered into the analysis separately were associated with increased risk of asthma diagnosis at 3–4 years. For example, the adjusted odds ratio for black carbon (per 10^{-5} increase in filter absorbance) was 1.14 (95% CI 1.01–1.29) [13]. Furthermore, there was a suggestion of a small independent effect of *in utero* exposure to air pollution. RYAN *et al.* [14] studied preschool wheezy children at increased risk of developing the classical school-age asthma phenotype, identified using the Asthma Predictive Index (API) developed by CASTRO-RODRIGUEZ *et al.* [15]. Exposure to traffic pollution (expressed as average daily elemental carbon attributable to traffic (ECAT)) was assessed using an air pollution model that extrapolated home exposure from several fixed monitoring sites. Since ECAT exposure at 6, 12, 24 and 36 months was highly correlated, only the 12-month exposure was used in the analysis. Persistent wheeze, defined as wheeze reported at 24 and 36 months, was associated with exposure to >75 percentile ECAT (OR 2.3, 95% CI 1.2–4.6). In this study, no evidence was found that the effect of air pollution on asthma development is limited to children with positive API since the odds ratio in this subgroup of children was no different (OR 2.2, 95% CI 1.2–4.0). NORDLING *et al.* [16] used an air pollution model to estimate the home exposure to traffic of 4,089 Swedish infants during the first year of life. Exposure to air pollution, expressed either as PM_{10}, NO_2 or NOx, was associated with persistent wheeze at 4 years of age (OR 1.60, 95% CI 1.09–2.23; for a 5th to 95th percentile difference in NOx) [16].

Cohort studies that straddle the preschool and school-age years suggest that fossil fuel air pollution is not only associated with the development of preschool asthma but also with the development of classical asthma. For example, my research group recruited a cohort of 4,400 children and surveyed parents when their children were 1–5 years of age (a random sample of 880 in each year group) and again when they were 4–7 years of age [17]. Home exposure was assessed using an air pollution model that estimated the dispersion of pollutants from roads using road emissions inventories and wind direction (fig. 1). The model estimated PM_{10} emitted from roads (primary PM_{10}). Although we found no association between primary PM_{10} and wheeze in the first survey, a significant association was found in the second survey (adjusted OR 1.28, 95% CI 1.04–1.58). Furthermore, there was an association between PM and incident (*i.e.* new-onset asthma) wheeze (OR 1.42, 95% CI 1.02–1.97) [17]. Similarly, MCCONNELL *et al.* [18] followed up a cohort of Californian preschool children for 3 years. Of 2,497 children, 120 developed asthma (*i.e.* new-onset asthma) by school age. Using modelled exposure to traffic-derived emissions, the study found a positive association for new onset-asthma (HR 1.51, 95% CI 1.25–1.81) [18]. Since children from more than one geographical area (between city) were recruited by MCCONNELL *et al.* [18], the role of background levels of pollution could be determined. Background NO_2 was associated with increased risk of new-onset asthma (HR 2.18, 95% CI 1.18–4.01) but this association was greatly reduced when modelled traffic exposure at both the home and school was included in the analysis [18]. Even though there may be publication bias for pollution studies, the consistency of these associations between studies suggests that traffic-derived pollutants are associated with the development of preschool wheeze. The mechanism whereby air pollution predisposes to the development of preschool wheeze remains unknown. It is however, unlikely to be *via* upregulation of allergic sensitisation or chronic eosinophilic airway inflammation, as these are not associated with wheeze in the preschool period. One possibility is that pollutants

predispose to viral infection of the lower respiratory tract [19], which in turn triggers attacks of preschool wheeze in children with a developmental impairment in airway mechanics.

If air pollution is associated with the development of school-age asthma, then associations between air pollution and new-onset disease should be found in older children and adults. JERRETT *et al.* [20] randomly selected a sample of 217 school-age children from 917 eligible subjects in a Southern California Children's Health study. Between 10 and 18 years of age there were 30 new cases of asthma. Children had NO_2 monitors (passive diffusion tubes) situated outside their homes for 2 weeks in the summer and 2 weeks in the autumn for the year 2000. In this study, home NO_2 reflected both exposure to local traffic emissions and NO_2 transported into the area from other regions. Despite the relative lack of accuracy of NO_2 for locally derived traffic pollution, a positive association was found (HR 3.25, 95% CI 1.35–7.86) for a 28 ppb increase in outdoor home NO_2 [20]. SHIMA *et al.* [21] recruited a cohort of 3,234 schoolchildren aged 6–9 years and surveyed them yearly for 4 years. Incident asthma was assessed in children with no symptoms in the first survey. For boys, living within 50 m of a heavily used road was associated with new-onset asthma (OR 3.77, 95% CI 1.0–4.99), with a non-significant but positive association for girls (OR 4.03, 95% CI 0.9–17). In adults, KUNZLI *et al.* [22] studied 2,725 never-smokers who were followed up for 11 years as part of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 1). Exposure to air pollution was assessed using a dispersion model. Data from fixed monitors were essential in the analysis since overall traffic emissions fell by 25% during the study period. Exposure was expressed as home outdoor traffic-related PM10 (TPM), similar to primary PM10 used in our previous study of preschool children [17]. New-onset asthma was associated with modelled exposure to TPM10 (HR 1.3, 95% CI 1.05–1.61) per 1 $\mu g \cdot m^{-3}$ change but interestingly distance from road *per se* was not associated with risk of new-onset asthma. Taken together, these studies suggest that air pollution from traffic does increase the risk of developing classical school-age asthma. Ideally, these data should be subject to a meta-analysis but the different ways of assessing exposure to traffic emissions is a barrier to developing an unbiased overview. The mechanism whereby air pollution predisposes to asthma remains unclear. It is unlikely to be acting *via* increased atopy since a recent systematic review of long-term prospective birth cohort studies found no association between traffic exhaust exposure and the development of allergic sensitisation [23].

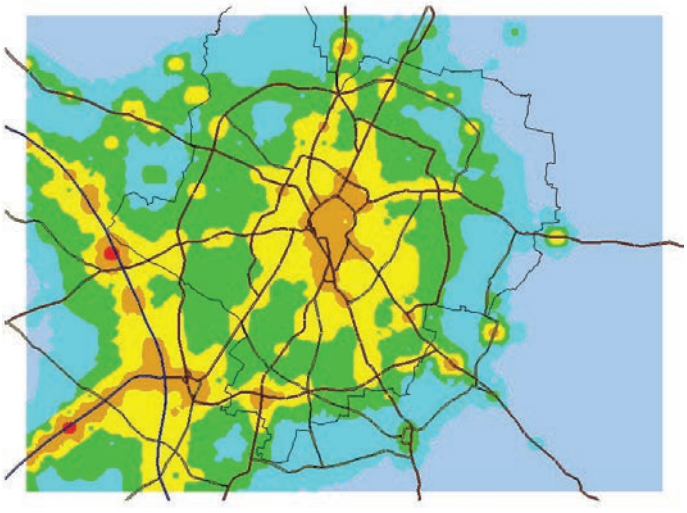

Figure 1. The output for mean annual primary PM10 (particles with a 50% cut-off aerodynamic diameter of 10 μm) for an urban area in the UK, generated using dispersion modelling. This output was used to assess the effects of traffic pollution on the development of wheeze in young children [17]. Higher levels of pollution are yellow/red and lower levels are blue. Areas of high exposure track with heavily used roads with hot spots at major junctions (lines). © Crown copyright Ordnance Survey, all rights reserved (NC/01/504).

Although it is very difficult in epidemiological studies to tease out whether road traffic effects are due to PM or NO_2 (or even some other closely associated pollutant), it is feasible to assess the effect of ozone. This is because the background concentration of ozone does not always track with background levels of primary pollutants. In the 12 Community Southern California study, 265 of 3,535 children reported a new diagnosis of asthma during a 5-year follow-up [24]. In communities with high background ozone concentrations, the relative risk of developing asthma in children playing three or more sports was 3.3 (95% CI 1.9–5.8). Additional analysis by ISLAM *et al.* [25] found that the risk of

developing asthma in these children was modified by functional polymorphisms in antioxidant genes (ozone is an oxidant gas). However, no effect of ozone could be detected in the 3-year follow-up of preschool children in the later Southern California children's health study (discussed previously), although this analysis did not include genotyping [24]. To date, the association between ozone, activity and new-onset asthma have not been replicated. Whether ozone increases the risk of asthma therefore remains unclear but is clearly of concern.

Could the association between air pollution and new-onset asthma be associated with new-onset allergic sensitisation? As discussed previously, atopy is not a major risk factor for preschool wheeze, but is a risk factor for asthma in the school-age period. To address this question, GRUZIEVA *et al.* [26] prospectively studied 4,089 Swedish children born between 1994 and 1996 for 8 years. Long-term exposure to locally generated air pollution (NO_2 and PM10) was determined by dispersion modelling. Exposure to locally generated air pollution was found to be associated with increased risk of pollen sensitisation at 4 years of age (OR 1.83) but at 8 years of age, no overall increase in sensitisation was found. These results suggest that it is unlikely that atopy is a driver for the association between incident school-age asthma and air pollution. In children with preschool wheeze there is good evidence that the effects of air pollution are independent of atopic status. For example, in a cross-sectional study of 150 children with preschool wheeze (aged 2–6 years) MCCORMACK *et al.* [27] found that the association between increased home PM and increased respiratory symptoms was independent of children's atopic status. Whether air pollution is associated with new-onset non-atopic school-age asthma remains unclear, but this is the logical conclusion from the prospective study of GRUZIEVA *et al.* [26].

Second-hand tobacco smoke and new-onset asthma

The association between second-hand smoke and new-onset asthma has been addressed by a recent meta-analysis of studies published between 1970 and 2005 [28]. The researchers identified 38 epidemiological studies, which included data on new-onset asthma in comparable groups (exposed/unexposed), with at least one source of postnatal second-hand smoke, for children 0–18 years of age. For incident asthma, the meta-regression used data from eight cohort studies. The predicted relative risk for a second-hand smoke effect on incident asthma, after adjusting for covariates, was 1.33 (95% CI 1.14–1.56) [28]. Mindful of the difference between preschool wheeze and school-age asthma, the researchers assessed the effect of age on this association. Remarkably, this association was not driven by wheeze in preschool children alone. Indeed, older children exposed to second-hand smoke were more, not less, likely to develop asthma, suggesting that new-onset classical asthma is associated with second-hand smoke [28]. The component of second-hand smoke responsible for this association is unclear but it interesting to note that second-hand smoke (essentially a biomass combustion pollutant) and traffic-derived pollution both contain aggregates of carbonaceous nanoparticles. It may therefore be more appropriate to combine second-hand smoke with proximity to traffic to produce a single exposure variable rather than adjust for second-hand smoke when assessing the effects of traffic emissions in epidemiological studies.

Indoor-generated NO_2 and new-onset asthma

Gas cooking and heating increases indoor NO_2. If NO_2, irrespective of source, has an adverse effect on asthma development, then one would expect that children living in homes using gas cooking/heating to be at an increased risk of new-onset wheeze. Indeed, studies into the effect of indoor gas combustion on asthma development offer a way of resolving the question of whether traffic-derived NO_2 is only a marker for the adverse health effects of PM. In Tasmania, a small proportion of families (2%) use portable- or fixed-type gas heaters but these heaters generate very high levels of indoor NO_2. PONSONBY *et al.* [29] linked data on gas heating exposure of 863 Tasmanian infants in the first weeks of life to reported asthma in these children when surveyed 7 years later as part of a larger study. Compared with families with electric heating, only children exposed to gas heaters

were at increased risk of asthma (RR 1.95, 95% CI 1.16–3.29) with no effects of open fire, oil heater, kerosene heater, or central heating of any type [29]. Indirect evidence that NO_2 has an independent effect on new-onset preschool wheeze is provided by a cross-sectional survey of 8,257 children less than 6 years old as part of the US Third National Health and Nutrition Examination Survey [30]. The prevalence of asthma was not only higher in children exposed to second-hand smoke (OR 1.8, 95% CI 1.2–2.6), but also those with use of a gas stove or oven for heat (OR 1.8, 95% CI 1.02–3.2) [30]. To date, there is insufficient depth of data to be confident that there is an independent effect of NO_2 on asthma development. However, they do suggest the view that PM accounts for all of the effects of NO_2 may be too simplistic. My own view is that very high levels of NO_2 may be associated with increased wheeze in young children, but at the more normal exposure levels associated with indoor cooking and proximity to traffic, it may, sensitise the airway to PM.

Statement of Interest

None declared.

References

1. Review of the UK air quality index. A report by the Committee on the Medical Effects of Air Pollutants. Health Protection Agency, 2011. www.comeap.org.uk/membership/130-review-of-the-uk-air-quality-index.html
2. House of Commons Environmental Audit Committee. Air Quality, fifth report of session 2009-10. Volume 1. London, The Stationery Office Limited, 2010. www.publications.parliament.uk/pa/cm200910/cmselect/cmenvaud/229/229i.pdf
3. Esplugues A, Ballester F, Estarlich M, *et al.* Indoor and outdoor concentrations and determinants of NO_2 in a cohort of 1-year-old children in Valencia, Spain. *Indoor Air* 2010; 20: 213–223.
4. BéruBé KA, Sexton KJ, Jones TP, *et al.* The spatial and temporal variations in PM10 mass from six UK homes. *Sci Total Environ* 2004; 324: 41–53.
5. Nawrot TS, Perez L, Kunzli N, *et al.* Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* 2011; 377: 732–740.
6. Asthma. still more questions than answers. *Lancet* 2008; 372: 1009.
7. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133–138.
8. Sunyer J, Puig C, Torrent M, *et al.* Nitrogen dioxide is not associated with respiratory infection during the first year of life. *Int J Epidemiol* 2004; 1: 116–120.
9. Gauderman WJ, Avol E, Gilliland F, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057–1067.
10. Gauderman WJ, Vora H, McConnell R, *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; 369: 571–577.
11. Matt GE, Hovell MF, Quintana PJ, *et al.* The variability of urinary cotinine levels in young children: implications for measuring ETS exposure. *Nicotine Tob Res* 2007; 1: 83–92.
12. Brauer M, Hoek G, Smit HA, *et al.* Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007; 29: 879–888.
13. Clark NA, Demers PA, Karr CJ, *et al.* Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010; 118: 284–290.
14. Ryan PH, Bernstein DI, Lockey J, *et al.* Exposure to traffic-related particles and endotoxin during infancy is associated with wheezing at age 3 years. *Am J Respir Crit Care Med* 2009; 180: 1068–1075.
15. Castro-Rodriguez JA, Cifuentes L, Rodriguez-Martinez CE. The asthma predictive index remains a useful tool to predict asthma in young children with recurrent wheeze in clinical practice. *J Allergy Clin Immunol* 2011; 127: 1082–1083.
16. Nordling E, Berglind N, Melen E, *et al.* Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 2008; 19: 401–408.
17. Pierse N, Rushton L, Harris RS, *et al.* Locally generated particulate pollution and respiratory symptoms in young children. *Thorax* 2006; 61: 216–220.
18. McConnell R, Islam T, Shankardass K, *et al.* Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect* 2010; 118: 1021–1026.
19. Wong CM, Thach TQ, Chau PY, *et al.* Part 4. Interaction between air pollution and respiratory viruses: time-series study of daily mortality and hospital admissions in Hong Kong. *Res Rep Health Eff Inst* 2010; 154: 283–362.
20. Jerrett M, Shankardass K, Berhane K, *et al.* Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008; 116: 1433–1438.
21. Shima M, Nitta Y, Adachi M. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan. *J Epidemiol* 2003; 13: 108–119.

22. Kunzli N, Bridevaux PO, Liu LJ, *et al.* Traffic-related air pollution correlates with adult-onset asthma among never-smokers. *Thorax* 2009; 64: 664–670.
23. Braback L, Forsberg B. Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. *Environ Health* 2009; 8: 17.
24. McConnell R, Berhane K, Gilliland F, *et al.* Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002; 359: 386–391.
25. Islam T, Berhane K, McConnell R, *et al.* Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 2009; 64: 197–202.
26. Gruzieva O, Bellander T, Eneroth K, *et al.* Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *J Allergy Clin Immunol* 2012; 129: 240–246.
27. McCormack MC, Breysse PN, Matsui EC, *et al.* Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol* 2011; 106: 308–315.
28. Vork KL, Broadwin RL, Blaisdell RJ. Developing asthma in childhood from exposure to secondhand tobacco smoke: insights from a meta-regression. *Environ Health Perspect* 2007; 115: 1394–1400.
29. Ponsonby AL, Couper D, Dwyer T, *et al.* The relation between infant indoor environment and subsequent asthma. *Epidemiology* 2000; 11: 128–135.
30. Lanphear BP, Aligne CA, Auinger P, *et al.* Residential exposures associated with asthma in US children. *Pediatrics* 2001; 107: 505–511.

Chapter 13

Psychological factors

James Paton

SUMMARY: There are a number of psychological factors that are recognised to be important in childhood asthma. Anxiety and depression are more common in children with asthma and are associated with worse asthma outcomes. Acute and chronic stresses, usually arising from a child's family environment, are associated with asthma exacerbations and worse asthma outcomes. While both depression and stress may affect asthma indirectly by impacting on asthma management, there is growing evidence of more direct effects mediated through changes in the immune system or *via* the autonomic nervous system.

Anxiety and depression are easy to miss clinically and are often overlooked. Clinicians looking after children with poorly controlled or difficult-to-control asthma need to be particularly alert because asthma control may not improve until psychological factors are addressed. Surprisingly, the evidence base for the effect of psychological interventions is very limited.

KEYWORDS: Anxiety, asthma, children, depression, psychological factors, stress

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It is 25 years since R.C. Strunk and co-workers published a seminal study of 21 children who died of asthma after discharge from hospital [1]. Compared with children matched for age, sex and asthma severity at the time of hospitalisation, STRUNK *et al.* [1] found 14 factors to be significantly different in the children who died, of which 10 related to psychological factors in the child or the child's family. The authors suggested that studying these psychological factors may be important in identifying children at high risk of dying from asthma and in developing treatment plans to prevent deaths from asthma [1].

The idea that psychological factors are important in asthma is not new and dates back to the 19th century. In fact, 100 years ago, psychological factors would have been considered key in asthma causation such that, in 1901, William Osler wrote in his classic text book, *The Principles and Practice of Medicine*: "all writers agree that there is in a majority of cases of bronchial asthma a strong neurotic element. Many regard it as a neurosis […] in which spasm results from disturbed innervation" [2].

Osler also recognised that "fright or violent emotion may bring on a paroxysm", acknowledging that psychological factors can have a role in asthma attacks [2].

Even up until the 1950s, the idea that atopic disorders including asthma and atopic dermatitis were "psychosomatic" and psychogenic in "origin" was commonplace. Psychoanalytic theories also viewed asthma as psychological in origin, with treatment involving analysis and other "talking cures" [3].

It is only in the last 40 years that the idea of asthma and related atopic disorders as inflammatory diseases has become the dominant paradigm. As a result, powerful and effective pharmacological therapies developed to control airway inflammatory processes are now in widespread use.

By chance, this changing view of asthma causation has coincided with substantial increases in the prevalence of atopic disorders in developed Western societies; some studies found one in three individuals have some form of atopic disease [4]. The causes for this ''epidemic of asthma and atopy'' have not been precisely identified [5, 6].

Nevertheless, it is now widely acknowledged that, despite great advances in pharmacological treatments, a substantial burden of asthma-related morbidity and mortality related to asthma continues [7–9]. While there are many reasons for poor asthma control [10], the mismatch between effective treatments and continuing morbidity has led to a reawakening of interest in non-pharmacological factors that potentially influence asthma control. These include factors such as non-adherence with treatment [11, 12], poor doctor–patient relationships, family functioning and social difficulties [13] and their impact on asthma, as well as the psychological problems highlighted by STRUNK *et al.* [1].

What are the psychological issues in children with asthma?

There is a substantial body of research in children and young people with asthma on the impact of mental health, and emotional and behavioural problems on functional status and asthma morbidity [14, 15].

Early studies in the field emphasised difficulties in separation from parents and associated anxiety. Later studies shifted to factors such as stress and medication management that could lead to adjustment difficulties [16]. In a meta-analysis, MCQUAID *et al.* [14] summarised the evidence from studies of behavioural adjustment in children and adolescents with asthma. In 28 studies with data from 5,000 children with asthma (mean age 8.4 years; 40% female), they found that children with asthma had more behavioural difficulties than healthy children [14]. Consistent with clinical impressions, they found that the effect was greater for ''internalising behaviours'' than for ''externalising behaviours'', *i.e.* children with asthma were more likely to exhibit anxious and depressive symptoms than oppositional or hyperactive symptoms. They also found that increased asthma severity was associated with greater behavioural difficulties.

Anxiety

There are good *a priori* reasons why asthma may be associated with anxiety [17]. Asthma, by its nature, can be a frightening and unpredictable illness. Acute asthma attacks, in particular, can be associated with unpleasant sensations such as choking or suffocation or hyperventilation-induced breathlessness and anxiety. In some individuals, these symptoms overlap with panic/fear symptoms such as being afraid of dying.

In animal studies in rats, fear of dyspnoeic suffocation induced by a single exposure to 100% carbon dioxide has been shown to be a conditioned (and hence learned) response [18]. This has led to the suggestion that at least some features of panic attacks in asthmatic patients may arise because of a conditioned response to breathlessness.

Anxiety through an effect on breathing may in turn lead to greater use of as-required asthma medication. In one study of adults with severe asthma being treated intensively in hospital, those with high levels of panic/fear symptoms were more likely to use as required bronchodilator medication [19]. In turn, asthma medications may make anxiety symptoms worse because of side-effects such as tremor. Many paediatricians treating children with problematic asthma will recognise similar problems in some children with excessive use of bronchodilator and associated side-effects.

Furthermore, asthma and anxiety have a number of risk factors in common including parental cigarette smoking [20] and stress during childhood, both of which seem to increase the risk of asthma onset and exacerbation [21, 22]. There is also evidence that social stress anxiety can promote and amplify airway inflammation in response to other asthma triggers [23].

In the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), anxiety is not one disorder but a spectrum of conditions [24]. Many of the studies in children and adults with asthma have focused on specific types of anxiety such as panic disorder, or social phobia in teenagers.

How common is anxiety in children with asthma?

KATON *et al.* [25] summarised the published data from the last two decades on the relationship between asthma and anxiety disorders in adults and children. In both adults and children, populations with asthma had a high prevalence of anxiety disorders. In seven studies in children/adolescents with asthma, up to one third of children met criteria for comorbid anxiety. In adult populations with asthma, the estimated range of panic disorder was between 6.5% and 24% [25].

KATON *et al.* [25] also highlighted a number of weaknesses in the published studies. For example, whether anxiety and asthma co-occur requires study designs that investigate populations which are not selected because they either have asthma or anxiety disorder. Studies in the field have frequently not used standardised measures of either asthma or anxiety and have not taken into account the probable confounding factors [26].

Another important criticism is that few studies attempt to separate out the potential overlap between symptoms of asthma and panic. Patients may have difficulty remembering or discerning which episodes were due to asthma, which to panic or a combination of both.

Much evidence has come from cross-sectional surveys using validated questionnaires or diagnostic interviews to assess the prevalence of the conditions in populations at a particular moment in time. Such approaches can show associations, but longitudinal cohort studies are needed to investigate causal relationships and the direction of causality. In fact, many of these very criticisms apply across the whole field of psychological factors and asthma in children. A number of more recent studies have addressed these points across the childhood age range.

Primary school children

VUILLERMIN *et al.* [17] found that Australian primary school children aged 5–13 years with asthma were at a substantially higher risk of anxiety than their non-asthmatic peers. This study used a population-based sampling approach with a high participation and response rate. It used a two-stage paediatric clinical assessment to confirm diagnosis of asthma, and two separate measures of anxiety status using the Spence Children's Anxiety Scale (SCAS; a child self-report measure and a parent report). Anxiety scores were higher in children with asthma than controls and were more likely to be in the clinical range (OR 2.5, 95% CI 1.1–5.8).

In the age range studied (mean 9.0, range 5.8–13.5 years), VUILLERMIN *et al.* [17] found that panic/agoraphobia, separation anxiety, generalised anxiety and obsessions/compulsions, but not social anxiety, were all more probable in children with asthma. Children with anxiety scores in the clinical range were more likely to be using asthma preventive medication and have greater school absence. In this population there was no difference between boys and girls [17].

Adolescents

In a telephone survey of children in a US health-maintenance organisation examining the relationship between youth-reported asthma symptoms and the presence of anxiety or depressive symptoms, RICHARDSON *et al.* [27] identified 125 children (aged 11–17 years) with asthma and at least one DSM feature of anxiety (panic, generalised anxiety, separation anxiety, social phobia or agoraphobia) and/or depression (major depression or dysthymia) in the last 12 months: 68 (8.9%)

with an anxiety disorder alone, 21 (2.5%) with a depressive disorder alone, and 37 (4.8%) with both an anxiety and a depressive disorder. After adjustment, these children reported significantly more days of asthma symptoms over the previous 2 weeks than those with no anxiety. There was evidence of a dose–response relationship, with the number of reported asthma symptoms significantly related to the number of anxiety and depressive symptoms reported by the child [27, 28]. The authors concluded that the presence of an anxiety or depressive disorder was highly associated with an increased asthma symptom burden; they suggested this was an additive effect of the anxiety and depression rather than increased severity of asthma in children with anxiety and depression.

Social anxiety may be a particular risk for adolescents with asthma with reports of feeling different and isolated from their peers, fearing peer rejection, having poor social competence and being additionally disadvantaged when asthma affected their ability to take part in activities such as sport or dance [29, 30].

In a large survey of predominantly white, middle-class students attending two US high schools (mean age 15.2 yrs, 77% female), BRUZZESE *et al.* [31] found that teenagers with asthma and current symptoms feared being viewed negatively by their peers and reported more generalised discomfort in social situations than those without asthma. However, the adolescents with asthma did not report increased fear of new situations and, in this study, there was no relationship between asthma severity and social anxiety. This suggested that the main concern for the adolescents in this study was managing any asthma in front of their immediate peer group [31]. Thus, in adolescents, social anxiety might affect medication compliance when medication is used in front of peers; for example, in using reliever medication before exercise [32].

Young adults

Many of the published studies of anxiety in asthma, including the ones mentioned previously, are cross-sectional studies. There are few longitudinal studies in the field.

One community-based prospective study in Switzerland followed 591 young people who were aged 19 years at enrolment, for over 20 years. The sample was enriched to include those at high risk of psychiatric disorders. Over 90% of the subjects completed at least two semi-structured interviews and almost half completed all six interviews, with professionals allowing longitudinal relationships between asthma and panic disorders to be investigated [33].

In the study, HASLER *et al.* [33] found that having asthma was associated with an increased chance of being diagnosed with anxiety or panic disorder, with evidence of a dose–response relationship. After adjusting for confounders, the investigators found that active asthma predicted subsequent panic disorder (OR 4.5). The authors also found evidence of the reverse association with more severe panic disorder (with recurrent unexplained panic attacks) predicting subsequent active asthma (OR 6.3).

Although validated psychological instruments were used, one problem with this study was that the diagnosis of active asthma was based on the subjects having doctor-diagnosed asthma and "asthma-like breathing problems" in the last year. The lack of an objective test, such as lung function, increases the possibility that some "asthma-like symptoms" might overlap with, or be mistaken for, panic and hyperventilation.

Despite some limitations, there is overall substantial evidence that anxiety is common in children with asthma and that it can contribute to an increased asthma symptom burden and worse asthma outcomes in affected children.

Depression

There is also a large body of research about the impact of depression in patients with asthma. The majority of the evidence originates largely from adult studies where the diagnosis of depression is easier to make, but many of the findings and themes are echoed in the smaller paediatric literature.

Again, it is important to highlight that many of the studies are both cross-sectional and retrospective, and that often both the definition and measurement of depression and asthma are unclear and not standardised [3].

OPOLSKI and WILSON [3] summarised the adult evidence about the association between asthma and depression as follows: 1) the evidence was mixed as to whether those with asthma were more likely to be depressed than those without; 2) the combination of asthma and depression may have an additive effect on asthma-related quality of life reductions; 3) subjective measures of asthma severity may be more related to depression than objective measures; 4) specific asthma symptoms, particularly dyspnoea, wakening at night and morning symptoms, appear to be linked to depression; 5) sadness and depression can produce respiratory effects consistent with asthma exacerbation; 6) depression can negatively affect asthma treatment compliance; 7) corticosteroid use in asthma has been associated with depression; and 8) interventions that address the physical, psychological and social consequences of asthma are likely to lead to the best treatment outcomes. In adults, both patient-reported depressive symptoms and physician-reported depressive conditions have been significantly associated with asthma severity. However, it is patient-reported depressive symptoms that associate more closely with asthma control [34].

In the paediatric literature, a meta-analysis summarised the evidence for an association between chronic illness, including asthma, and depression. BENNETT [35] reviewed 60 studies of depressive symptoms among children and adolescents with chronic medical problems and concluded that children with a chronic medical problem were at a slightly elevated risk of depressive symptoms but that most were not clinically depressed. While there was considerable variability in depressive symptoms in children with the same disorder, children with certain disorders (*e.g.* asthma, recurrent abdominal pain and sickle cell anaemia) appeared to be at a greater risk than children with other disorders (*e.g.* cancer, cystic fibrosis and diabetes mellitus) [35].

A longitudinal cohort study of more than 1,000 children in New Zealand, who were followed for 21 years, examined the link between depressive and anxiety disorders and asthma [36]. Asthma in adolescence and young adulthood was associated with an increased likelihood of major depression (OR 1.7, 95% CI 1.3–2.3), panic attacks (OR 1.9, 95% CI 1.3–2.8) and any anxiety disorder (OR 1.6, 95% CI 1.2–2.2). This study is interesting for two reasons. First, further analysis suggested that the association between asthma and depressive anxiety symptoms was most likely to reflect common factors associated with both asthma and depressive and anxiety disorders. The factors examined included family socioeconomic disadvantage, family instability and conflict, child abuse and parental adjustment problems, and particularly drug and alcohol abuse and criminality. Secondly, the odds ratios reported are very similar to a large World Health Organization (WHO) survey of over 85,000 adults in 17 countries. This survey reported an age-adjusted and sex-adjusted odds ratio of mental disorders among people with self-reported asthma relative to those without, of 1.6 (95% CI 1.4–1.8) for depressive disorders and 1.5 (95% CI 1.4–1.7) for anxiety disorders [37]. This relationship was present across the different countries and ethnic groups studied.

Depression has also been reported to be common in children presenting with acute exacerbations. In a study of children (aged 7–17 years) from an inner city background recruited in emergency rooms at the time of an acute asthma exacerbation (AAE), depressive symptoms were reported in approximately 25% of children and just under half of mothers. Self-reported depressive symptoms were more strongly associated with the child's asthma activity than either parental or parental/clinician ratings of the child's depression [38].

There is also a body of evidence about the acute effects of emotions on children with asthma. In short-term laboratory studies of children (aged 8–17 years) with moderate-to-severe asthma watching scenes from the movie ET (selected to evoke sadness, happiness or a mixture of the two), sadness was found to be associated with greater heart rate variability and instability of oxygen saturation compared with happiness; mixed results were found for the happy/sad scenes. This led the authors to propose a general model whereby psychobiological effects from depressed

emotional states may affect asthma activity by causing autonomic dysregulation [39, 40]. They suggest that increased cholinergic activation in states of depression, hopelessness and despair may negatively interact with cholinergically mediated airway reactivity in asthma; vulnerability might be short lived, as in watching the scenes from the movie, or longer lived, as might occur in clinical depression. This takes us back to Osler's idea of spasm resulting from disturbed innervation mentioned at the beginning of the chapter.

The impact of the caregiver's mental health and adverse family environments

The previous evidence focuses on the individual relationship between asthma and depression. There is abundant evidence that childhood asthma is strongly affected by family factors, such as the psychological functioning of the parents and interactions between the parent and child, independent from the child's own functioning and adjustment [41]. Some families may be particularly at risk for difficulties in managing asthma because of problems in their particular family social environment or because of risk factors related to social stressors such as poverty [41]. Three particular areas can be highlighted as follows.

Caregiver's mental health

KAUGARS *et al.* [41] highlighted that poorer caregivers' psychological functioning is associated with worse asthma outcomes in the children [41]. For example, in a US study around 50% of mothers of children with asthma living in urban inner city environments reported high levels of depressive symptoms. In the following 6 months, mothers with higher levels of depressive scores were 40% more likely to have taken their children to the emergency department than less depressed mothers [42]. This echoes the findings of WAXMONSKY *et al.* [38] that depressive symptoms were common in children presenting with AAE and their mothers.

In the prospective National Cooperative Inner-City Asthma Study, WEIL *et al.* [13] found that psychosocial factors, particularly the caregiver's mental health, had the strongest relationship to children's asthma morbidity. Children whose caregivers had clinically significant levels of mental health problems were hospitalised for asthma at almost twice the rate of children whose caregivers did not. Children with clinically significant behavioural problems had significantly more days of wheeze and poorer functional status in the follow-up period. The authors concluded that psychosocial factors, particularly the mental health of children and caregivers, were significant factors in predicting asthma morbidity [13]. Similarly, in US suburban and inner city paediatric asthma subspecialty practices, children were more likely to have high morbidity, based on symptoms and healthcare use, if they had caregivers with more depressive symptoms and negative life stressors, and if they were female [43].

Family conflict

Family conflict was one of the issues that identified children who died of asthma in the seminal study by R.C. Strunk of deaths in childhood due to asthma [1]. Patient–parent conflict reflecting long-standing parent–child problems was identified either in the medical records or directly, as persistent or severe arguments and clashes that were noted during parental visits or telephone calls. This negative behaviour was common in the interactions of families of children who subsequently died, but occurred in only approximately 25% of the control families [1]. CHEN *et al.* [44] also found that in children hospitalised with asthma and then followed prospectively for 1 year, the lifetime history of hospitalisations was associated with family impacts (greater family strain and family conflict, greater financial strain), as well as caregiver characteristics (greater personal strain, beliefs about not being able to manage their child's asthma).

Early-life parenting difficulties and the development of asthma

Caregivers' responses to high chronic stress levels may affect not only their own psychological functioning but also have an impact on respiratory problems in their children. In a birth cohort

study, WRIGHT *et al.* [21] reported that greater levels of caregiver-perceived stress at 2–3 months were associated with increased risk of subsequent repeated wheeze among the children during the first 14 months of life (RR 1.6, 95% CI 1.3–1.9), even after controlling for factors potentially associated with both stress and wheeze, as well as mediators through which stress might influence wheeze (maternal smoking, breastfeeding, indoor allergen exposures and lower respiratory infections). Furthermore, caregiver stress prospectively predicted wheeze in the infants, whereas wheeze in the children did not predict subsequent caregiver stress. The effect of caregiver stress on early childhood wheeze was independent of caregiver smoking and breastfeeding behaviour, as well as allergen exposure, birth weight and lower respiratory infections [21].

Therefore, it is clear that the mental health of caregivers and family stresses are potentially important psychological factors affecting asthma in children.

Psychological stress and life events

A common adverse psychological factor emerging from the evidence about caregivers' mental health and family problems is the role of stress. While there has been a long-standing belief that acute psychological stress, such as that induced by fright or violent emotions, can trigger an asthma attack [22], it is only recently that convincing scientific evidence has accumulated that confirms this fact [45].

Stress occurs when demands from the environment challenge a person's ability to cope [46]. When stress is appraised as threatening by an individual, it elicits a psychological response composed of negative cognitive and emotional states [46], responses that can have biological and behavioural consequences.

Negative ''stressors'' can include major life events that are relatively rare, such as the death of a parent or close relative, but require major adjustment; chronic stressors include exposure to violence or family conflict, or more common events that are part of everyday life such as sitting an exam or daily hassles. Stressors are commonly classified as either acute (time-limited in duration with a clear onset and offset, *e.g.* sitting an exam) or chronic (related to ongoing life difficulties with no clear end-point in sight) [45]. Both have been linked to changes in the human immune system, although the direction of change can vary depending on the stressor, or whether the person is healthy or suffers from an illness such as asthma.

Psychological stress has generally been conceptualised in two ways [47]. The environmental stress conceptualisation focuses on the demands of everyday events that individuals encounter as part of their life experience. Such stresses have to be managed but are assumed to have a fairly uniform effect on people's health. Research in this area has exploited commonly occurring stressful situations, such as school exams, that arise in children and young people's lives. For example, LIU *et al.* [48] showed that students undergoing a final examination had higher anxiety and depression scores and an enhanced eosinophilic response to antigen challenge during the examination period. This approach commonly uses checklists to objectively enumerate the stresses that a person has experienced over a certain time frame.

The alternative conceptualisation focuses on an individual's response to stress, appraising how a person perceives the stressor, whether they perceive it as a threat and whether they can cope with it effectively. This approach commonly uses questionnaires or interviews of individuals to focus on both the event and the subjective perception of the event. One widely quoted study used an interview schedule involving both parents and their children to investigate the impact of stress on children with asthma [22]. In an 18-month study of children with asthma, SANDBERG *et al.* [22] found that the experience of a severely negative life event (*e.g.* death of a close family member) increased the risk of an asthma attack nearly two-fold. When the event occurred against the backdrop of high chronic stress, the risks of an exacerbation were accentuated and occurred earlier. Children exposed to high levels of acute and chronic stress showed a three-fold increase in risk for an attack in the 2 weeks that followed the acute event.

Pathways and mechanisms

At present there is no clear understanding of the pathways and mechanisms that link psychological states and problems to the onset, severity or course of asthma. There has been a debate about whether the effects of psychological factors occur through indirect or direct effects.

Indirect effects

Indirect effects are mediated through secondary pathways whereby factors such as depression and stress alter behaviour in ways that lead to worse asthma outcomes. These include effects on factors such as treatment adherence that negatively impact on asthma control, and effects on the symptom perception (symptoms, peak flow, *etc.*). In some older children and adults, these behaviours may also lead to other dysfunctional coping behaviours, such as increased smoking and alcohol consumption, which, in turn, eventually alter immune responses.

A possible theoretical framework model that illustrates the potential interrelations between mental health and asthma outcomes is shown in figure 1.

In this model, KATON *et al.* [25] propose that anxiety and depressive illness as well as asthma severity-related factors may undermine health behaviours such as self-efficacy, locus of control and self-esteem, which are important for asthma control. Both asthma and anxiety symptoms can lead to frightening thoughts with a sense of being out of control and needing help.

Because children have higher levels of intrinsic airways resistance, negative stressors and mood states may be more likely to cause significant changes in resistance, undermining self-confidence in learning to master these conditions. Indeed, there is experimental evidence that asthmatic children show a greater response to a short stress than normal controls [49]. The combination of frightening thoughts with a decreased confidence and sense of control may then affect active self-management tasks such as taking medications. This in turn worsens asthma-symptom burden and results in increased healthcare utilisation and cost. Anxiety and depressive symptoms may also

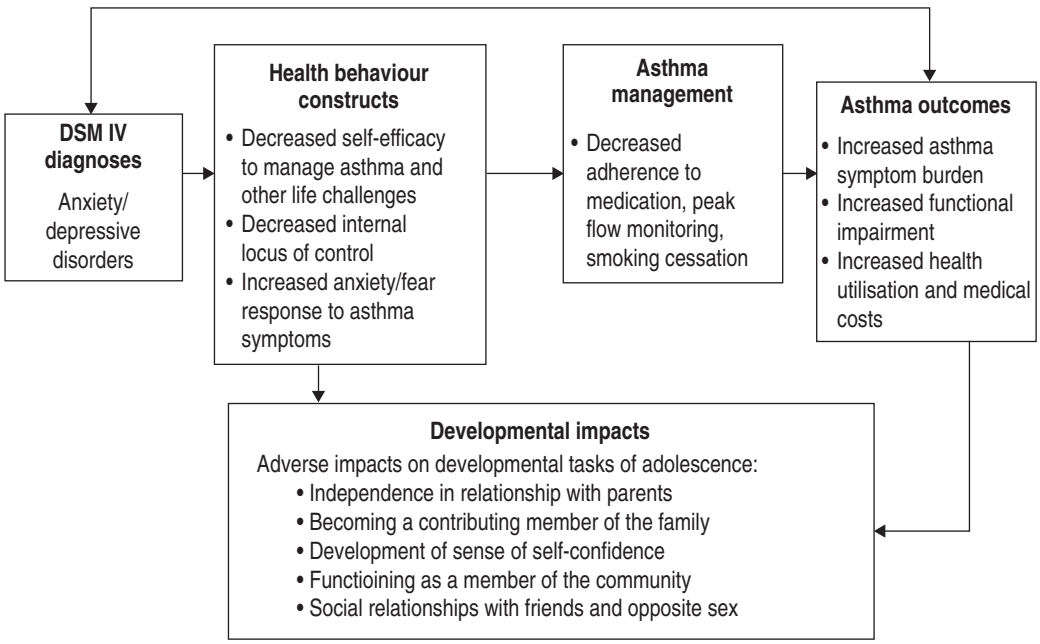
DSM IV diagnoses
Anxiety/ depressive disorders
Health behaviour constructs
• Decreased self-efficacy to manage asthma and other life challenges
• Decreased internal locus of control
• Increased anxiety/fear response to asthma symptoms
Asthma management
• Decreased adherence to medication, peak flow monitoring, smoking cessation
Asthma outcomes
• Increased asthma symptom burden
• Increased functional impairment
• Increased health utilisation and medical costs
Developmental impacts
Adverse impacts on developmental tasks of adolescence:
• Independence in relationship with parents
• Becoming a contributing member of the family
• Development of sense of self-confidence
• Functioining as a member of the community
• Social relationships with friends and opposite sex

Figure 1. Adverse impact of anxiety/depressive disorders and asthma comorbidity. DSM: Diagnostic and Statistical Manual of Mental Disorders. Reproduced and modified from [25] with permission from the publisher.

directly affect the perception of asthma symptoms [13]. Anxiety, in particular, is commonly associated with hyperventilation and other dysfunctional breathing patterns. These functional breathing problems can result in asthma-like symptoms and can act as a trigger for asthma [50].

The final point for growing children is that anxiety/depression and asthma, both separately and when combined, may negatively affect fundamental developmental key tasks, particularly in adolescents.

Direct effects

The alternative possibility is that psychological effects may have a more direct impact, altering the magnitude of the inflammatory airway response. CHEN and MILLER [45] have proposed that psychological stress operates by modulating the magnitude of the airway response that irritants, allergens and infections can bring about in individuals with asthma. These effects are mediated through increases in airway inflammation and it is this that leads to increases in the frequency and severity of asthma symptoms (fig. 2).

The model suggests two possible biological pathways to airway inflammation and bronchoconstriction paths. The first is a psychoneuroimmunological pathway where stress alters immune inflammatory processes [45]. A second path acts *via* psycho-physiological effects mediated through the autonomic nervous system (ANS) (fig. 3) [40]. Here hopelessness/depression/despair act to disrupt ANS regulation by tilting the balance between sympathetic and parasympathetic activity. MILLER *et al.* [40] have presented evidence in children with asthma and high depression scores showing a preponderance of vagal over sympathetic activity in responses to laboratory-induced emotional stress. In contrast, children with asthma without depression showed a greater preponderance of sympathetic activity [49, 51].

MILLER and CHEN [52] point out that there is a paradox here because exposure to stress would be expected to activate both the hypothalamic pituitary and the sympathetic adrenal medulla axes, leading to increased secretion of hormones (cortisol, epinephrine and nor-epinephrine). High levels of these molecules should suppress inflammation and cause bronchodilatation. However, long exposure to stress hormones may lead to down-regulation of receptors, and a decreased response to asthma triggers.

MILLER and CHEN [52] have extended their work by looking for molecular evidence linking measures of acute and chronic stress in children with the expression of mRNA for the glucocorticoid receptor (GR) and the β_2-adrenergic receptor (β_2-AR). They found that chronic stress was associated with reduced expression of mRNA for β_2-AR among children with asthma compared with an opposite effect in healthy children. Children with asthma who simultaneously experienced acute and chronic stress exhibited a 5.5-fold reduction in GR mRNA and a 9.5-fold

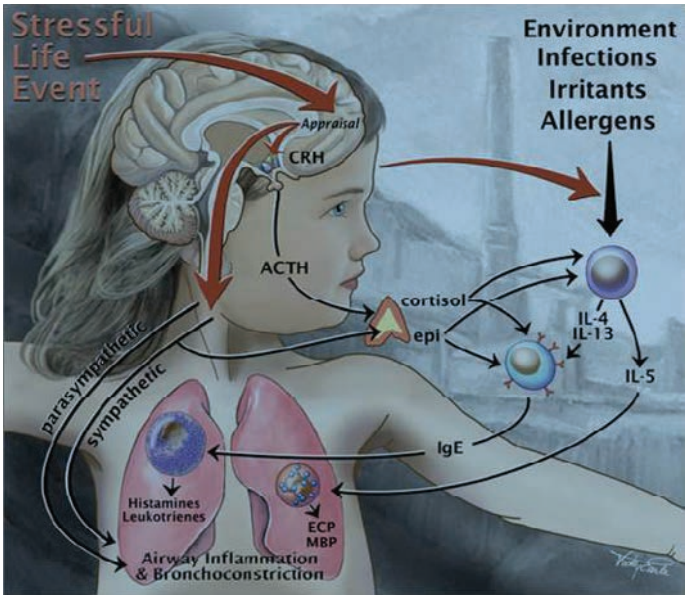

Figure 2. Model depicting the interaction of psychological stress with environmental triggers in influencing asthma exacerbations. CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropin hormone; epi: epinephrine; IL: interleukin; Ig: immunoglobulin; ECP: eosinophilic cationic protein; MBP: major basic protein. Reproduced from [45] with permission from the publisher.

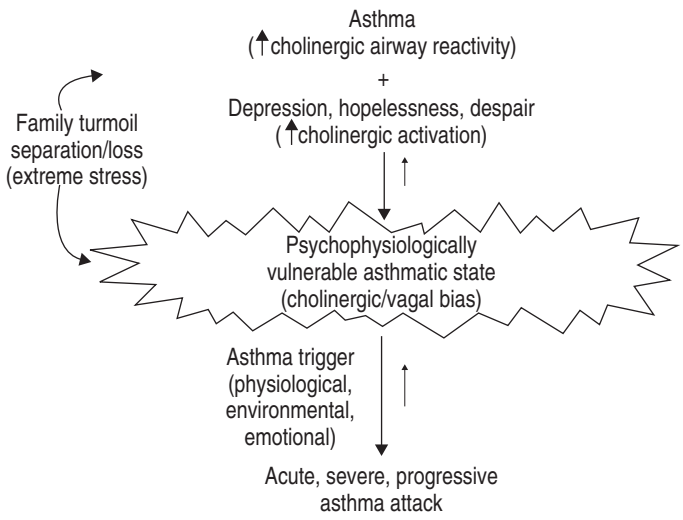

Figure 3. Autonomic dysregulation model of emotional influence on asthma. Reproduced and modified from [40] with permission from the publisher.

reduction in β_2-AR mRNA compared to children with asthma without comparable stressor exposure.

These findings provide persuasive experimental support that stressful experiences downregulate gene expression in a way that could explain the increased asthma morbidity associated with stress. The same authors have also shown that in children with asthma the larger social environment can affect processes at the genomic level, with gene transcription control pathways that regulate inflammation and catecholamine signalling varying by socioeconomic level in children with asthma. Because these pathways are the primary targets of many asthma medications, these findings suggest that the larger social environment may alter molecular mechanisms that have implications for the efficacy of asthma therapeutics [53].

Bidirectional effects

There is a large body of evidence in children documenting an association between asthma and psychological issues, such as anxiety and depression. Much of this data is based on cross-sectional studies with few longitudinal studies. The question that then arises is: does having asthma predispose to psychological dysfunction or is it that psychological dysfunction leads to asthma?

A recent meta-analysis examined prospective studies investigating the influence of psychosocial factors on atopic disorders, particularly asthma, as well the effect of atopic disorders on mental health. This confirmed that the evidence suggested a robust relationship between psychological factors and asthma, and that this effect was bidirectional. Psychosocial factors were adversely involved in the development and prognosis of atopic disorders but there was also strong evidence of effects of atopic disorders on mental health. The authors concluded that there was robust evidence of bidirectional effects, particularly in children [54]. In a separate analysis, they found psychological distress and poor social support, but not exposure to stressors that included life events or daily stress had a significant adverse impact on atopic disorders. The authors concluded that clinical approaches that focused on managing the emotional reaction and organising social support were likely to be more useful approaches than attempting to prevent stress exposure.

Implications for clinical practice

Diagnosis

While alert clinicians may recognise psychological issues in children with asthma during review, routine assessment of psychological and emotional well-being is not currently a standard part of paediatric care, either in community-based settings or hospitals [50]. There is a particular issue with ''internalising disorders'' such as anxiety, and depression that can often go unrecognised during a short medical consultation in both children and adults [55]. This is particularly likely when the primary focus of the consultation is another clamant physical problem such as asthma.

Because psychological factors are common and because of their potential to interact negatively with a child's asthma, either directly or through behavioural pathways, clinicians always need to be alert to the possibility that psychological factors may be contributing to a child's current asthma symptoms and control. This is particularly true in the case of children with problematic or difficult-to-control asthma.

Assessment for psychological issues can take several forms. It could be a few, brief open-ended questions to evaluate child adjustment and family coping. In a difficult-to-control clinic it may be appropriate to use screening instruments (such as the SCAS [56] or the Hospital Anxiety and Depression Scale (HADS)) to help recognise those children with significant levels of anxiety and depression. Most children will not reach levels of psychiatric "caseness"; those who do can be referred for more detailed mental health assessment and treatment.

Since psychological circumstances can change over time, this should not be a single-point-of-time assessment but a continuing evaluation as a child grows and develops. It may be particularly important to be alert at potentially stressful developmental transitions, such as after a move to a new school environment (*e.g.* from primary school to high school) or after known life events such as a death in the family. VUILLERMIN *et al.* [17] have highlighted that children who miss a substantial amount of time from school may be at particular risk of comorbid anxiety.

Treatment strategies

If the child has a major comorbid psychiatric condition, such as clinical depression, or a major anxiety state, then referral to a mental health professional will be appropriate.

Children who present with complex medical and psychosocial profiles, such as the child whose anxiety about asthma symptoms is affecting school attendance, may be best managed by a multidisciplinary team approach wherein medical and psychosocial personnel establish a collaborative family-treatment approach. GODDING *et al.* [57] provided evidence for the effectiveness of such an approach which involved a joint consultation between a paediatrician and a child psychiatrist in 41 high-risk asthmatics and their families. 2 years after the onset of the joint consultation, a significant improvement was found in symptom score, treatment score and compliance score. The number of hospital admissions and the number of days spent in hospital decreased significantly [57]. For paediatricians and specialists who do not have immediate access to mental health professionals within their own practice environments, establishing relationships with mental health providers who are familiar with the psychological consequences of chronic illness issues, which may be critical for effective treatment planning.

However, the evidence outlined above suggests that lesser degrees of anxiety and depression occur frequently in asthma. Since asthma symptoms may also limit physical, emotional and social aspects of a child's life, a child's psychological status may both be a consequence of and contribute to asthma morbidity. Because of these reciprocal links, studies have investigated whether psychological interventions might be beneficial in the treatment of asthma, irrespective of whether there is any *a priori* evidence of psychological distress or impaired psychosocial function [58].

Psychological interventions that might be used include behavioural therapies, cognitive therapies, cognitive behavioural therapy (CBT), relaxation techniques, psychodynamic psychotherapies and counselling, in both individual and group formats [58]. The British Thoracic Society (BTS) guidelines note that limited studies on hypnosis and family therapy suggest some possible benefits from these interventions [59]. Breathing retraining exercises include a range of techniques for improving breathing control in asthma (*e.g.* Buteyko technique, yoga and transcendental meditation). They are not regarded as standard psychotherapies, although aspects of these approaches may be included in behavioural therapy or CBT [60].

A systematic review of psychological interventions in children with asthma included only 12 studies and reported that the studies were small and the standard was poor [61]. For example, the

psychological approaches used were varied, they did not necessarily have a clear theoretical underpinning, and they were not always well described. While the authors acknowledged that psychological problems needed to be identified and addressed as part of asthma management, from their review they were unable to draw firm conclusions about the potential positive benefits of psychological interventions in children with asthma. The evidence in adults is, surprisingly, similarly limited [61, 62].

VAN LIESHOUT and MACQUEEN [58] have noted that because of problems with selecting children with asthma who might benefit, as well as the limited availability of trained therapists, there may be many children with poor asthma control related to psychological factors who might benefit but are routinely not even offered therapies because of the lack of a sound evidence base about effective interventions. It would be difficult to envisage an area where a stronger evidence for treatment is needed.

Prospects for prevention

Just as adverse events and experience may worsen childhood asthma there is some evidence that positive events may have a positive effect and counteract a child's reaction to more negative circumstances [63]. SANDBERG *et al.* [63] followed 90 children with asthma and found that, provided they occurred in close proximity to severely negative life events, positive life events generally related to a child's own achievements gave protection against the increased risk of asthma exacerbations precipitated by severely negative life events. This effect was only seen in children exposed to low to medium levels of stress and not if the stress level was high and the exposure chronic [63].

This points to a more general question: why do some individuals thrive and not get sick despite exposure to persistent and severe adversities, a quality labelled as resilience? [64].

CHEN *et al.* [64] have highlighted that although children with asthma from backgrounds of lower socioeconomic status have more symptoms and more severe exacerbations, and are more likely to have unscheduled healthcare visits for asthma, some children living in such circumstances have good asthma control [65]. In a prospective study, CHEN *et al.* [64] identified one psychological strategy contributing to resilience, "shift and persist", that protected those children living in low-socioeconomic status homes from adverse asthma outcomes. In this strategy, children who used it dealt with stresses by reframing stressors more positively while at the same time persisting in optimistic thoughts about the future. These children had less asthma inflammation at baseline, as well as less asthma impairment in terms of reduced rescues inhaler use and less school absence after 6-months' follow-up [64].

This raises the possibility of using or enhancing psychological qualities already present within a child to mitigate the effects of adverse psychological factors that may impact on asthma.

Conclusion

It is increasingly clear that although asthma may have genetic and allergic origins, psychosocial factors have a very important impact on many aspects of the disease. Although the body of literature in children is smaller than in adults, there is still abundant evidence about the importance of psychological factors, particularly anxiety and depression, and psychological stress on both the impact of asthma and its causation. There is evidence that children with anxiety and depression experience more symptoms and have worse outcomes, such mental health problems may often go unrecognised and the role of psychological therapies is uncertain. While concerns about the role of psychological factors in asthma may have been around for over a century it is clear that much remains to be learned. The prospects for advancing the health and well-being of children with asthma seem, potentially, to be quite large.

In the meantime, paediatricians need to be aware of the possibility that psychological factors may be important, particularly in those with poor asthma control.

Statement of Interest

None declared.

References

1. Strunk RC, Mrazek DA, Fuhrmann GS, *et al.* Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985; 254: 1193–1198.
2. Osler W. The Principles and Practice of Medicine. 4th Edn. New York, D. Appleton and Co., 1901.
3. Opolski M, Wilson I. Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clin Prac Epidemiol Ment Health* 2005; 1: 18.
4. Asher MI, Montefort S, Bjorksten B, *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 733–743.
5. Shafazand S, Colice G. Asthma: the epidemic has ended, or has it? *Chest* 2004; 125: 1969–1970.
6. Holgate ST. The epidemic of asthma and allergy. *J R Soc Med* 2004; 97: 103–110.
7. Braman SS. The global burden of asthma. *Chest* 2006; 130: Suppl. 1, 4S–12S.
8. Demoly P, Gueron B, Annunziata K, *et al.* Update on asthma control in five European countries: results of a 2008 survey. *Eur Respir Rev* 2010; 19: 150–157.
9. Poulos LM, Toelle BG, Marks GB. The burden of asthma in children: an Australian perspective. *Paediatr Respir Rev* 2005; 6: 20–27.
10. Haughney J, Price D, Kaplan A, *et al.* Achieving asthma control in practice: understanding the reasons for poor control. *Respir Med* 2008; 102: 1681–1693.
11. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? *Ann Allergy Asthma Immunol* 1997; 79: 177–185.
12. Bender B, Milgrom H, Rand C, *et al.* Psychological factors associated with medication nonadherence in asthmatic children. *J Asthma* 1998; 35: 347–353.
13. Weil CM, Wade SL, Bauman LJ, *et al.* The relationship between psychosocial factors and asthma morbidity in inner-city children with asthma. *Pediatrics* 1999; 104: 1274–1280.
14. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. *J Dev Behav Pediatr* 2001; 22: 430–439.
15. Wamboldt MZ, Fritz G, Mansell A, *et al.* Relationship of asthma severity and psychological problems in children. *J Am Acad Child Adolesc Psychiatry* 1998; 37: 943–950.
16. Klinnert MD, McQuaid EL, McCormick D, *et al.* A multimethod assessment of behavioral and emotional adjustment in children with asthma. *J Pediatr Psychol* 2000; 25: 35–46.
17. Vuillermin PJ, Brennan SL, Robertson CF, *et al.* Anxiety is more common in children with asthma. *Arch Dis Child* 2010; 95: 624–629.
18. Mongeluzi DL, Rosellini RA, Caldarone BJ, *et al.* Pavlovian aversive context conditioning using carbon dioxide as the unconditional stimulus. *J Exp Psychol Anim Behav Process* 1996; 22: 244–257.
19. Dahlem NW, Kinsman RA, Horton DJ. Panic-fear in asthma: requests for as-needed medications in relation to pulmonary function measurements. *J Allergy Clin Immunol* 1977; 60: 295–300.
20. Hedman L, Bjerg A, Sundberg S, *et al.* Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. *Thorax* 2011; 66: 20–25.
21. Wright RJ, Cohen S, Carey V, *et al.* Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. *Am J Respir Crit Care Med* 2002; 165: 358–365.
22. Sandberg S, Paton JY, Ahola S, *et al.* The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356: 982–987.
23. Haczku A, Panettieri RA Jr. Social stress and asthma: the role of corticosteroid insensitivity. *J Allergy Clin Immunol* 2010; 125: 550–558.
24. American Pyschiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th Edn. Arlington, American Pyschiatric Association, 1994.
25. Katon WJ, Richardson L, Lozano P, *et al.* The relationship of asthma and anxiety disorders. *Psychosom Med* 2004; 66: 349–355.
26. Goodwin RD. Asthma and anxiety disorders. *Adv Psychosom Med* 2003; 24: 51–71.
27. Richardson LP, Lozano P, Russo J, *et al.* Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. *Pediatrics* 2006; 118: 1042–1051.
28. McCauley E, Katon W, Russo J, *et al.* Impact of anxiety and depression on functional impairment in adolescents with asthma. *Gen Hosp Psychiatry* 2007; 29: 214–222.
29. Kyngas H. Support network of adolescents with chronic disease: adolescents' perspective. *Nurs Health Sci* 2004; 6: 287–293.

30. Kyngas H. Compliance of adolescents with chronic disease. *J Clin Nurs* 2000; 9: 549–556.
31. Bruzzese JM, Fisher PH, Lemp N, *et al.* Asthma and social anxiety in adolescents. *J Pediatr* 2009; 155: 398–403.
32. Randolph CC, Fraser B. Stressors and concerns in teen asthma. *Allergy Asthma Proc* 1998; 19: 193–203.
33. Hasler G, Gergen PJ, Kleinbaum DG, *et al.* Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med* 2005; 171: 1224–1230.
34. Mancuso CA, Wenderoth S, Westermann H, *et al.* Patient-reported and physician-reported depressive conditions in relation to asthma severity and control. *Chest* 2008; 133: 1142–1148.
35. Bennett DS. Depression among children with chronic medical problems: a meta-analysis. *J Pediatr Psychol* 1994; 19: 149–169.
36. Goodwin RD, Pine DS, Hoven CW. Asthma and panic attacks among youth in the community. *J Asthma* 2003; 40: 139–145.
37. Scott KM, Von Korff M, Ormel J, *et al.* Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry* 2007; 29: 123–133.
38. Waxmonsky J, Wood BL, Stern T, *et al.* Association of depressive symptoms and disease activity in children with asthma: methodological and clinical implications. *J Am Acad Child Adolesc Psychiatry* 2006; 45: 945–954.
39. Miller BD, Wood BL. Influence of specific emotional states on autonomic reactivity and pulmonary function in asthmatic children. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 669–677.
40. Miller BD, Wood BL, Lim J, *et al.* Depressed children with asthma evidence increased airway resistance: ''vagal bias'' as a mechanism? *J Allergy Clin Immunol* 2009; 124: 66–73.
41. Kaugars AS, Klinnert MD, Bender BG. Family influences on pediatric asthma. *J Pediatr Psychol* 2004; 29: 475–491.
42. Bartlett SJ, Kolodner K, Butz AM, *et al.* Maternal depressive symptoms and emergency department use among inner-city children with asthma. *Arch Pediatr Adolesc Med* 2001; 155: 347–353.
43. Shalowitz MU, Berry CA, Quinn KA, *et al.* The relationship of life stressors and maternal depression to pediatric asthma morbidity in a subspecialty practice. *Ambul Pediatr* 2001; 1: 185–193.
44. Chen E, Bloomberg GR, Fisher EB Jr, *et al.* Predictors of repeat hospitalizations in children with asthma: the role of psychosocial and socioenvironmental factors. *Health Psychol* 2003; 22: 12–18.
45. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun* 2007; 21: 993–999.
46. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991; 325: 606–612.
47. Schreier HM, Miller GE, Chen E. Clinical potentials for measuring stress in youth with asthma. *Immunol Allergy Clin North Am* 2011; 31: 41–54.
48. Liu LY, Coe CL, Swenson CA, *et al.* School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med* 2002; 165: 1062–1067.
49. McQuaid EL, Fritz GK, Nassau JH, *et al.* Stress and airway resistance in children with asthma. *J Psychosom Res* 2000; 49: 239–245.
50. Thomas M, Bruton A, Moffat M, *et al.* Asthma and psychological dysfunction. *Prim Care Respir J* 2011; 20: 250–256.
51. Kullowatz A, Rosenfield D, Dahme B, *et al.* Stress effects on lung function in asthma are mediated by changes in airway inflammation. *Psychosom Med* 2008; 70: 468–475.
52. Miller GE, Chen E. Life stress and diminished expression of genes encoding glucocorticoid receptor and β2-adrenergic receptor in children with asthma. *Proc Natl Acad Sci USA* 2006; 103: 5496–5501.
53. Chen E, Miller GE, Walker HA, *et al.* Genome-wide transcriptional profiling linked to social class in asthma. *Thorax* 2009; 64: 38–43.
54. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med* 2008; 70: 102–116.
55. Katon W, Roy-Byrne P. Anxiety disorders. efficient screening is the first step in improving outcomes. *Ann Intern Med* 2007; 146: 390–392.
56. Spence SH, Barrett PM, Turner CM. Psychometric properties of the Spence Children's Anxiety Scale with young adolescents. *J Anxiety Disord* 2003; 17: 605–625.
57. Godding V, Kruth M, Jamart J. Joint consultation for high-risk asthmatic children and their families, with pediatrician and child psychiatrist as co-therapists: model and evaluation. *Fam Process* 1997; 36: 265–280.
58. Van Lieshout RJ, Macqueen G. Psychological factors in asthma. *Allergy Asthma Clin Imunol* 2008; 4: 12–28.
59. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the Managment of Asthma: A National Clinical Guideline. 2011. www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%Sept%2011.pdf
60. Holloway E, Ram FS. Breathing exercises for asthma. *Cochrane Database Syst Rev* 2004; 1: CD001277.
61. Yorke J, Fleming SL, Shuldham C. A systematic review of psychological interventions for children with asthma. *Pediatr Pulmonol* 2007; 42: 114–124.
62. Yorke J, Fleming SL, Shuldham CM. Psychological interventions for adults with asthma. *Cochrane Database Syst Rev* 2006; 1: CD002982.

63. Sandberg S, McCann DC, Ahola S, *et al.* Positive experiences and the relationship between stress and asthma in children. *Acta Paediatr* 2002; 91: 152–158.
64. Chen E, Strunk RC, Trethewey A, *et al.* Resilience in low-socioeconomic-status children with asthma: adaptations to stress. *J Allergy Clin Immunol* 2011; 128: 970–976.
65. Matthews KA, Gallo LC, Taylor SE. Are psychosocial factors mediators of socioeconomic status and health connections? A progress report and blueprint for the future. *Ann NY Acad Sci* 2010; 1186: 146–173.

Chapter 14

Airway hyperresponsiveness in children

*Jolt Roukema**, *Peter Gerrits*[#] *and Peter Merkus**

SUMMARY: Airway hyperresponsiveness (AHR) is a hallmark of asthma, but may also exist in children and adults with other lung disorders. It reflects an abnormal response with airway narrowing following exposure to a wide variety of non-sensitising stimuli of chemical or physical origin. The response may be abnormally sensitive: the degree of airway narrowing may increase markedly with increasing stimuli, and may result in complete airway closure. This abnormal response may be due to the presence of airway inflammation, abnormal airway mechanics or a combination of both. The airway challenge tests are subdivided into direct and indirect challenges. The direct challenges mainly have an effect on airway smooth muscle and, as such, predominantly reflect airway mechanics, whereas AHR assessed from indirect tests correlate better with the degree of airways inflammation. Therefore, direct and indirect tests are not interchangeable. AHR assessment is helpful for the diagnosis of asthma, but the role of routine AHR assessment in the management of children with asthma is unclear. In specific groups of children with asthma, knowledge of the degree of AHR may help to optimise individual treatment.

KEYWORDS: Airway hyperresponsiveness, asthma, bronchoconstriction, bronchoprovocation testing, hyperreactivity, lung function

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Airway hyperresponsiveness (AHR) is usually defined as abnormal sensitivity of the airways to narrow following a wide variety of non-sensitising stimuli of chemical or physical origin [1]. AHR seems a more adequate definition than bronchial hyperresponsiveness (BHR) since all airways are involved.

Stimuli may be direct or indirect, may be normal stimuli that exist in daily life, or may consist of compounds that are exclusively administered in the pulmonary function laboratory.

The end-point that is used to quantify the airway response is usually a common lung function parameter (most often forced expiratory volume in 1 second (FEV_1)) but may also be a measure

of airway resistance or transcutaneous oxygen saturation (*e.g.* for subjects unable to actively participate in lung functions tests or for research purposes).

Hence, the classification of AHR is based on a test and a standardised cut-off level is used for that particular test. In fact, it is not abnormal that subjects respond with airway narrowing following these provocation tests because these tests will ultimately lead to a response in all subjects. It is the degree and ease with which they respond that defines the response as abnormal. AHR is a characteristic feature of asthma and is found in almost all asthmatic patients, and in several other respiratory disorders.

Following administration of the stimulus, the response (usually a ventilator function parameter) is recorded. A dose–response curve can be obtained from every type of bronchoprovocation test, for which the dose is often log transformed. AHR (the sensitivity) is defined as the provocative dose (PD) or provocative concentration (PC) of the stimulant that results in a change in the end-point of a predetermined magnitude, a threshold (*e.g.* often a 20% fall in FEV_1), calculated through interpolation in the log-linear dose–response curve (fig. 1). Thus, AHR based on inhalation of methacholine or histamine is often quantified using the PD or PC causing a 20% decrease in the baseline lung function parameter (PD_{20} or PC_{20}) (fig. 1). Based on exercise testing, exercise-induced bronchoconstriction (EIB) is identified by documenting a fall in FEV_1 of $\geqslant$10% from the pre-exercise FEV_1 value within 20–30 minutes following exercise. The lowest values are usually measured within 5–12 minutes following the exercise test.

Typically, the dose–response curve in normal subjects may demonstrate a plateau. The dose–response curve in asthmatic subjects may be shifted to the left, indicating increased sensitivity, and may demonstrate a steeper slope, indicating hyperreactivity, with a higher plateau or even an immeasurable plateau, indicating an exaggerated maximal response (fig. 1).

Hence, AHR simply reflects the extent and ease with which airways will respond by narrowing following exposure to inhaled irritants or physical stimuli, such as exercise testing. As such, it is a hallmark of asthma, although AHR does not equal asthma and not all patients with asthma have AHR [2]. Therefore, a proper understanding of AHR seems fundamental to an understanding of the origin of asthma [3].

In addition, AHR is a dynamic phenomenon: it varies over time within patients. AHR is also found in patients with chronic obstructive pulmonary disease (COPD) (usually with a clear plateau of the dose–response curve) and in association with other respiratory disorders, such as bronchopulmonary dysplasia (BPD) [4, 5], cystic fibrosis [6], allergic rhinitis [7–9], and active or passive smoking [10, 11]. AHR may be partly determined genetically [12, 13] and can be regarded as a complex interaction between airway smooth muscle function,

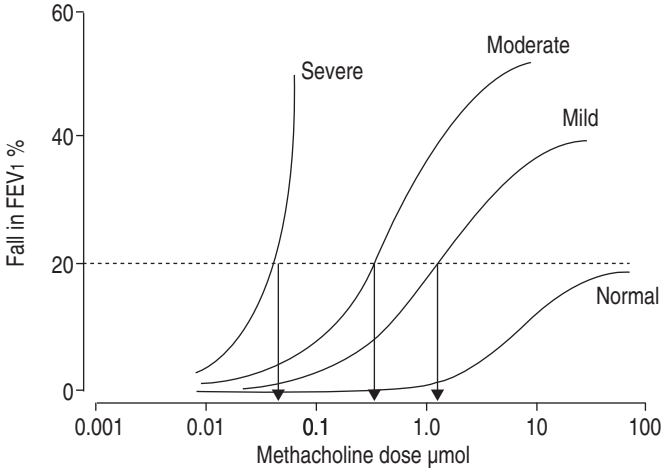

Figure 1. Schematic representation of the dose–response curves observed in normal subjects and severe, moderate and mild asthmatic subjects. The provocative dose causing a 20% decrease in baseline forced expiratory volume in 1 second (FEV_1) is lowest for all the asthmatic patients and is not reached in the normal subjects. It is calculated through interpolation of the concentration–response relationship. A similar concentration–response curve can be obtained, that results in a provocative concentration causing a 20% fall in FEV_1. For mannitol challenges, a cumulative dose of mannitol leading to a decrease of 15% in of baseline FEV_1 is used, which is also calculated through interpolation. The arrows indicate provocation dose or concentration.

airway inflammation and airway mechanics. In addition, the effector organ (being largely determined by airway smooth muscle) may exhibit an altered response to stimuli, and this may act independently from airway inflammation, as has been demonstrated in healthy subjects; simply changing the breathing pattern by avoiding deep breaths may affect AHR [14]. Indeed, deep inspirations have a protective effect against hyperresponsiveness in healthy subjects. In patients with asthma, this effect is modified by the disease. This is easily understood when summarising the possible mechanisms of AHR.

Possible mechanisms of AHR

The cause of airway narrowing following bronchial challenge tests is not simply the combination of constriction due to airway smooth muscle and oedema of the airway wall; it is much more complex. The possible mechanisms that play a role in AHR, irrespective of the nature of the agent or trigger leading to airway narrowing, were very well explained and summarised in an article by STERK and BEL [1]. The authors made a distinction between pre-junctional mechanisms, which lead to an augmentation of the stimulus, and post-junctional mechanisms, which lead to an increased response of the effector organ (table 1).

Pre-junctional mechanisms are circumstances that will facilitate the impact of the stimuli, and will lead to an augmentation of the stimuli. The result is a shift of the dose–response curve to the left, indicating that the patient is more sensitive to the stimuli and has increased AHR [1]. Typical examples of increased AHR due to pre-junctional mechanisms are those following exposure of children with allergic asthma to inhaled allergens, or following viral respiratory infections [15], passive smoking [11, 16] or outdoor pollution [17, 18].

Post-junctional mechanisms lead to an increased response of the effector organ. They are responsible for excessive airway narrowing in AHR. Typical examples of an increased response are: hyperplasia or hypertrophy of airway smooth muscle in asthma (resulting in increased contractility); oedema of the airway mucosa and/or of the adventitial layer in asthma that will markedly affect airway patency following bronchoconstriction; increased amounts of airway secretions in symptomatic asthma; or a loss of alveolar attachments as occurs following antenatal passive smoking [15, 19], in severe asthma [15, 19, 20], or in children with BPD [21].

Table 1. Examples of mechanisms that are potentially involved in airway hyperresponsiveness

Pre-junctional mechanisms: augmentation of stimuli	Post-junctional mechanisms: increased responses
Epithelial damage or malfunction	Smooth muscle contractility (smooth muscle hypertrophy and/or hyperplasia)
Altered neural control	Viscous and elastic loads (including decreased or loss of alveolar attachments or cartilage, and increased airway wall compliance)
Increased inflammatory cell number	Swelling of the airway wall (submucosa and adventitial layer)
Increased inflammatory cell activity	Intraluminal exudates and secretions
Interaction of inflammation and neural control	
Airway metabolism or absorption (affecting concentrations of mediators)	

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Another example is the effect of diminished counteracting forces as occurs in adventitial oedema due to mitral valve disease [22, 23], or increased compliance of the airways due to various reasons (remodelling and inflammation) [24].

Very interesting model studies have elaborated on these factors and their interactions [24–26]. Because of these factors, the log dose–response curves in

symptomatic patients with asthma differ from those in normal subjects with respect to their position, slope and maximal response. Following adequate anti-inflammatory treatment, AHR improves, which is reflected by a rightward shift of the curve with a less steep slope and a measurable and/or lower plateau.

Researchers have speculated that much more information is available when studying the whole dose–response curve instead of merely reporting the sensitivity, and that specifically addressing pre-junctional and post-junctional mechanisms might have therapeutic consequences and benefit the patient. However, in many cases, the pre-junctional and post-junctional mechanisms are interrelated (such as is the case in any inflammatory process in the airways), and there is probably a large heterogeneity of airway narrowing across the bronchial tree, which complicates the interpretation of the response.

In most cases, AHR is caused by airway inflammation and this results in an exaggerated response, as well as hypersensitivity, with both being highly correlated. Indeed, in patients with severe asthma, AHR and symptoms are highly correlated, especially in cross-sectional studies where AHR is closely correlated with asthma severity [27].

In daily patient care of children with asthma, the result of the bronchoprovocation test is equal to sensitivity but, the maximal response is actually much more important. The possibility of excessive airway narrowing makes AHR potentially dangerous and life-threatening. The presence of a plateau indicates that there is a maximal response, irrespective of the strength of the stimulus, and that the patient is somehow protected against (progressive) airway closure. Indeed, the lack of a plateau on the dose–response curve implies that absolute and progressive airway closure will occur as long as the stimuli are active; this may be what happens in many children with severe or fatal asthma.

Figure 2 illustrates that forced vital capacity (FVC) may be markedly reduced following airway narrowing due to a bronchoprovocation test performed in a child with asthma, simply indicating a loss of lung volume due to airway closure. The maximal expiratory flow–volume curve of the patient also illustrates that peak expiratory flow (PEF) may be normalised while FVC is not. This also

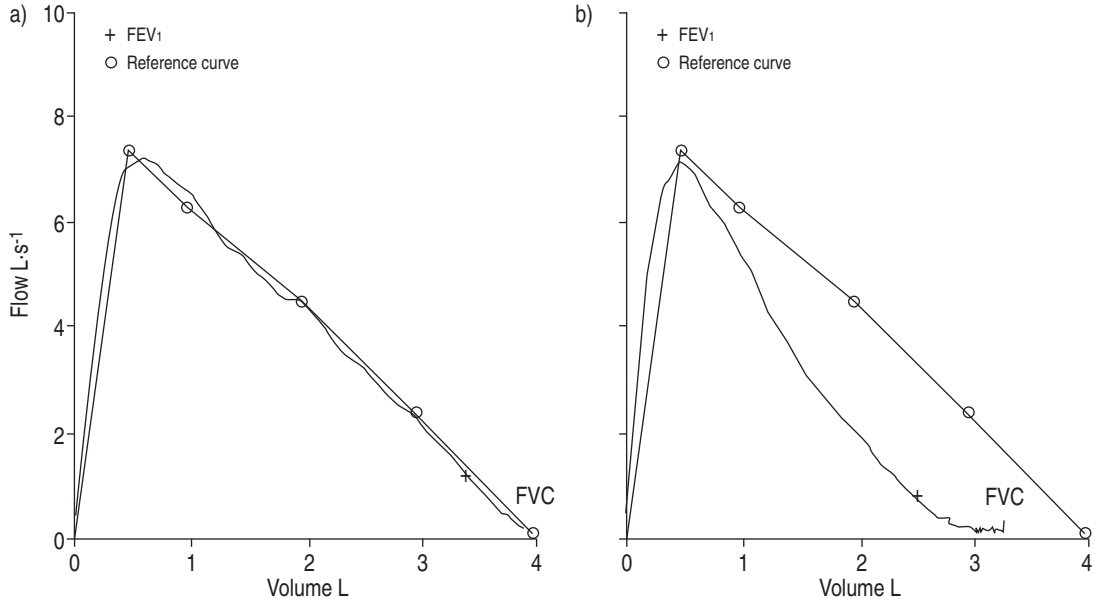

Figure 2. Two maximal expiratory flow–volume (MEFV) curves from a child with asthma. a) MEFV curve prior to bronchoprovocation with histamine. b) MEFV curve after clinical recovery of a histamine provocation test. Peak expiratory flow has restored, but forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are still diminished. Note: the loss of >0.5 L FVC indicates airway closure.

illustrates that PEF is not a sensitive marker of peripheral airway function as PEF does not reflect peripheral airway patency and is only weakly correlated with FEV_1. As a result, the use of PEF as an end-point in airway challenge testing is not recommended as a very sensitive measure of AHR. In fact, in a young patient who suffered a fatal asthma episode, PEF was not affected by peripheral airways obstruction in spite of severe symptoms and did not reveal that bronchodilators failed to improve peripheral airways obstruction (fig. 3) [28]. In a laboratory study, it was demonstrated that excessive airway narrowing in asthma occurs to a similar degree in children as to that found in adults [29].

Histological consequences of inflammation-induced AHR

AHR may be accompanied by long-term histological changes that are partly reversible. The reversible conditions are related to factors such as active inflammation that can be redressed through anti-inflammatory treatment, whereas the irreversible histological changes consist of sub-endothelial thickening, smooth muscle hypertrophy, altered matrix composition and vascular changes [30]. Obviously, such airway remodelling may simply be the result of long-standing inflammation. As airway remodelling may negatively affect airway patency and airway mechanics [24, 26], it may cause AHR to persist for many years and/or become worse. This seems to explain AHR as a risk factor for a less favourable outcome of asthma [31]. In addition, a (probably irreversible) loss of alveolar attachments has been documented in severe asthma [20]; this will also augment AHR.

Medication antagonising AHR

All compounds that decrease bronchomotor tone and/or reverse airway inflammation and/or oedema are potentially able to antagonise AHR. Short- and long-acting bronchodilators are able to shift the dose–response curve to the right quickly (within minutes/hours), but will not markedly affect the steepness of the slope or the maximal response. For this reason, maintenance treatment

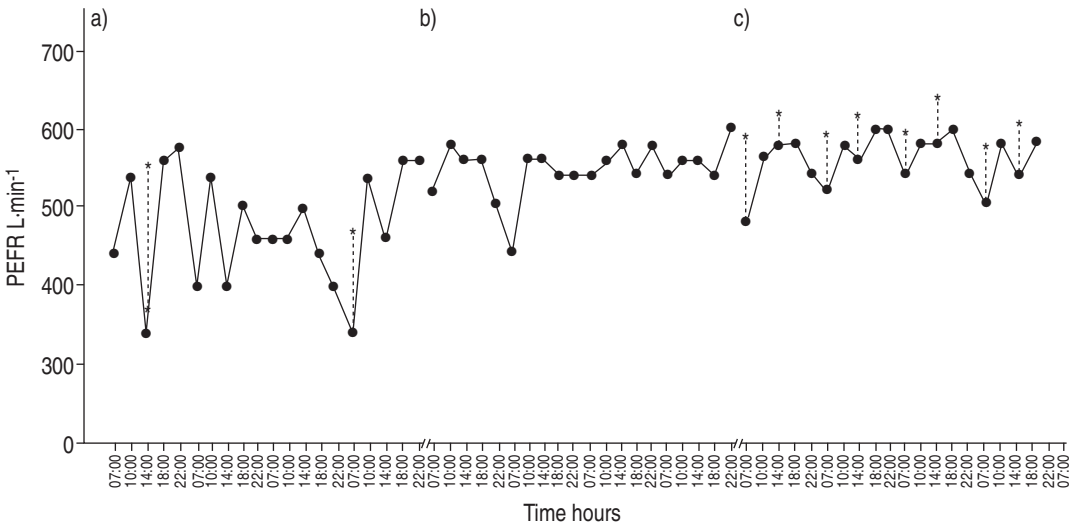

Figure 3. Peak expiratory flow rates (PEFR) at 07:00, 10:00, 14:00 and 22:00 hours during a) the first 4 days of treatment, b) 4 days of the following week (beclomethasone 0.5 mg *b.i.d* and fenoterol when required), and c) the last 4 days before the fatal attack (beclomethasone 1 mg *b.i.d* and fenoterol 0.4 mg *b.i.d*). The daily variability of PEFR at each respective time-point was: a) 41, 26, 20 and 39% (mean value=32%); b) 14, 21, 7 and 10% (mean value=13%); and c) 17, 13, 10 and 14% (mean value=14%). The reversibility to fenoterol was a) 62 and 35% (mean value=49%) and c) 23, 7, 13, 9, 10, 14 and 11% (mean value=12%). Dotted lines and asterisks represent reversibility to fenoterol. Reproduced from [28] with permission from the publisher.

using bronchodilators and without adequate anti-inflammatory treatment in patients with asthma constitutes a serious health risk. Anti-inflammatory compounds will generally slowly (after weeks/months) affect airway sensitivity, airway reactivity and the maximal degree of airway narrowing (*i.e.* position of the plateau of the dose–response curve).

When testing AHR in the laboratory, it is common practice to discontinue most or all medication affecting AHR (table 2) [32].

Following the bronchoprovocation tests, it is common practice to administer a bronchodilator or wait for spontaneous recovery of airway function to baseline level before discharging the child. For histamine challenge tests, the recovery process following airway narrowing has been studied, but little is known or documented about the recovery from indirect challenge tests.

The recovery from a histamine challenge was found to be related to the maximal dose administered, and to the degree of airway response [33]. Other studies found that the time to recovery following histamine challenge tests was related to the PD_{20} [34]. Several authors concluded that other tests can be conducted reliably, provided that FEV_1 has returned to at least 95% of the baseline value [34, 35].

Epidemiology of AHR: relationships with allergy, lung function and symptoms

Most studies on AHR were conducted using direct airway challenge tests, with either histamine or methacholine. Many epidemiological studies on AHR have been conducted in children and adults from a general population, and in groups of patients with asthma. Several studies have demonstrated a close relationship between development of allergy and asthma, and AHR [36, 37]. From longitudinal studies it has become clear that allergy is an important risk factor for the development of AHR [37–39], whereas AHR is a risk factor for the development and outcome of asthma [31]. AHR is also associated with a lower level of lung function after adolescence [40] and with an increased rate of annual decline of lung function in adults with asthma [40, 41].

AHR has been demonstrated in infancy, and has been shown to be increased in infants with a family history of asthma and/or those exposed to passive smoking [42]. Sometimes, evidence of AHR is already present prior to the diagnosis of asthma [43].

Higher FEV_1 values in childhood are associated with less severe AHR at 32–42 years of age, independent of other potential risk factors. At 32–42 years of age, a low level of lung function and the presence of asthma symptoms are associated with more severe AHR. A lower lung function in childhood and less improvement in FEV_1 over time are associated with more severe AHR in adulthood [31]. In a study on the relationship between atopy, respiratory symptoms, AHR and airway calibre in children with asthma, CLOUGH *et al.* [44] found that atopy was associated with lower FEV_1, AHR, greater daily PEF variation, and other symptoms.

Table 2. Medication that decreases or antagonises airway hyperresponsiveness (AHR)

Medication/food or drink	Minimal time between last dose and AHR measurement
Short-acting β_2-agonists	8 hours
Long-acting β_2-agonists	48 hours
Ipratropium bromide	24 hours
Theophylline	12 hours
Sustained-release theophylline	48 hours
Cromolyn sodium	8 hours
Nedocromil sodium	48 hours
Antihistamines	72 hours
Leukotriene antagonists	24 hours
Cola drinks, chocolate, coffee and tea (all caffeine- or theine-containing beverages)	Day of the study

(Inhaled) corticosteroids will affect AHR but are usually not discontinued, depending on the clinical question asked. Modified from [32], with permission from the publisher.

In two large descriptive studies in children and adolescents with asthma, it was demonstrated that the correlation between PEF and AHR was weak [45], also longitudinally [46]. Symptoms, AHR and PEF provide additional information about the condition of the patient, and PEF may be a relatively insensitive measure of AHR. Circadian variations in AHR have been described in adults and children with asthma [47, 48].

Direct and indirect tests

There are various types of challenges, and these are not interchangeable. A distinction is made between indirect and direct challenges. Indirect challenges include those with physical stimuli such as exercise, non-isotonic aerosols (hypertonic saline, distilled water and mannitol), cold dry air and pharmacological agents, such as adenosine monophosphate, sodium metabisulfite, tachykinin and bradykinin. Indirect challenges act by instigating the release of endogenous mediators that cause the airway smooth muscle to contract. This may induce or augment the inflammatory process in the airway wall [49]. This is in contrast with the direct challenges where agonists such as methacholine or histamine cause airflow limitation predominantly or exclusively *via* a direct effect on airway smooth muscle. Both direct and indirect challenges have been standardised to a great extent [50]. Most research on AHR in children has been conducted using indirect tests; in adults, most studies have used direct airway challenge tests.

Direct challenges

In a clinical population, direct challenges have a high sensitivity and a high negative predictive value for the diagnosis of asthma, which make them suitable as a test to exclude current asthma in a clinical population. In population studies, however, the tests are less useful for detecting asthma because of low specificity [51].

Direct bronchial responsiveness is only slowly influenced by administration of inhaled steroids [52, 53].

Indirect challenges

Indirect bronchial stimuli (in particular, exercise) hyperventilation and hypertonic aerosols, as well as adenosine, may reflect the ongoing airway inflammation more directly [54, 55] and are therefore more specific for detecting active asthma. They may reflect acute changes in airway inflammation more closely [56], and a change in AHR to an indirect stimulus may be a clinically relevant marker to assess the course of asthma within patients. Moreover, some of the indirect challenges, *e.g.* hypertonic saline and mannitol, can be combined with the assessment of inflammatory cells by induction of sputum. Indirect challenges are increasingly used to evaluate the prevalence of AHR and to assess specific problems in patients with known asthma, *e.g.* EIB, and evaluation before scuba diving.

Thus, direct and indirect challenges identify different abnormalities of the airways [57]. Because the results of direct and indirect challenges provide different and, to some degree, contradictory information, it has been recommended that both tests be conducted in patients with asthma to assess the contribution of airway mechanics and the degree of inflammation [49, 58, 59]. Various direct and indirect tests were also described by GODFREY *et al.* [60], including cut-off points for children and young adults with and without asthma.

Clinical use of AHR

The improvement of AHR in children with asthma following anti-inflammatory treatment was first described more than two decades ago [52]. One of the first long-term studies on this topic in children with asthma showed that the gradual improvement of AHR continues over a period of

several years under treatment with inhaled corticosteroids (ICS) [53]. Cessation of that treatment in children clearly and quickly resulted in deterioration [61]. Since then, many more studies have confirmed the favourable effects of anti-inflammatory treatment on the course of asthma in children [62].

Diagnostic purposes

In routine patient care, assessment of AHR may be useful as a tool for asthma diagnosis. When the history is atypical, AHR measurements may provide additional diagnostic information. However, AHR varies over time and not all children with asthma have AHR all of the time [2].

Monitoring purposes

Numerous studies in adults with asthma have indicated that AHR assessment should not be ignored as it provides additional information, alongside functional abnormalities and information about inflammatory markers [59]. However, the routine use of AHR measurements is not incorporated into guidelines for asthma management. The reason for this is a lack of evidence of a clear favourable long-term effect on outcome. Although it has been hypothesised that improvement of AHR is required in order to improve long-term prognosis in asthma [63], too few studies have been conducted to test that hypothesis.

In adults, it was demonstrated that treatment guided by regular monitoring of AHR to methacholine is superior to standard care because it is associated with improvement of histological, functional and clinical parameters [64]. In children with asthma, a similar study was conducted, demonstrating that AHR-guided treatment did not result in fewer symptom-free days but was associated with an improvement in baseline FEV_1 [65]. This finding may also indicate that, especially in children with a poor perception of dyspnoea (''poor perceivers''), assessment of AHR may be helpful in monitoring the disease [65].

In addition, there may be more categories of children with asthma in whom there is additional clinical value for assessing AHR as a part of the monitoring routine [1]. In children with symptomatic asthma, in spite of adequate anti-inflammatory treatment, the persistence of AHR for histamine may be used as an argument to introduce treatment with long-acting bronchodilators, while in children with poorly controlled asthma associated with more evidence of persisting airway inflammation (*e.g.* by high exhaled nitric oxide fraction ($F_{E}NO$) values) and little or no AHR, this may be a reason to intensify anti-inflammatory treatment (personal observations of the authors). However, to our knowledge, such applications of airway challenges in clinical decision making have not been validated by randomised longitudinal studies, and these need to be investigated further before they can be applied in routine care [2]. Similarly, a positive indirect challenge test and a negative or nearly normal direct challenge test provide further information on both the pathogenesis and the potential role of anti-inflammatory agents in its treatment [58].

The main indications for AHR testing in children and the contra-indications for airway challenges are listed in table 3. The most important indications for bronchoprovocation in children are: to rule out or support the diagnosis of asthma, to assess its severity and/or treatment effects, to monitor the disease, to help understand mechanisms of other diseases, and to assess the epidemiology of asthma [66]. According to previously published recommendations [66], classification of AHR severity for methacholine is possible (table 4).

Standardisation

Although Hippocrates was already aware that people with asthma suffer from an increased sensitivity for certain triggers, it was only in 1941 that DAUTREBANDE and PHILIPPOT [67] first published findings that asthmatics were more sensitive to the inhalation of histamine and

Table 3. Contra-indications for airway hyperresponsiveness testing

Moderate to severe airways obstruction: FEV_1 <60% pred or <1.5 L
Inability to perform acceptable quality spirometry
Acute viral infections of upper or lower airways
Unstable cardiac ischaemia, uncontrolled hypertension, malignant arrhythmias

FEV_1: forced expiratory volume in 1 second; % pred: % predicted. Reproduced and modified from [32] with permission from the publisher.

methacholine than healthy subjects. One of the first published studies on standardised broncho-provocation tests in adults used histamine [68]. Since then, various methods have been described for conducting airway challenge tests in adults [3, 69] and consensus statements have been published [70, 71]. Other reviews have specifically addressed the indirect challenges [3, 49, 58]. For children aged ⩾6 years, these have been adopted with minor changes, if any.

Many, if not all, aspects of the laboratory tests have been studied with respect to variability, and have been standardised as much as possible to minimise variability. It appears that room temperature and nebuliser characteristics co-determine the output of nebulisers [72, 73], and that nebuliser output is not constant over the years, possibly due to general wear to the plastic or the deposition of salt crystals [74, 75]. In addition, inhalation pattern also has a significant effect on the lung deposition of the agonist and, thus, on PC_{20} and PD_{20} [75]. In addition, the time interval between inhalation of the irritant and the subsequent lung function measurement is of relevance in assessing the response [76]. Consequently, the results of AHR by various inhalation devices differ and are not interchangeable; this explains the difficulty of comparing the results obtained with the dosimeter method with those obtained with the tidal breathing method [77].

As a result, there are major variations in protocol, different ethical requirements in different countries, and the suitability method differs according to the circumstance. This is perhaps not clinically relevant because, as for many biomedical signals, individual trends of AHR, as well as a patient's personal best value, will inform best about the condition of the patient. However, these differences will certainly complicate the comparisons between centres and will hamper the progress of epidemiological studies and knowledge of AHR [78].

The protocols of the most important challenges are briefly summarised in table 5. For detailed information, the reader is referred to the appropriate references.

Some specific comments are required for exercise testing. Exercise testing may be one of the easiest tests to perform, but it may also be more complex than anticipated. It might not be informative to run or cycle when the symptoms appear during skating. The tests could be conducted outdoors, preferably using the same exercise routine that produces the patient's symptoms, for as long as necessary, with a handheld spirometer if available. When the water content in air is too high, a false-negative test may be obtained. The best circumstances are available when the water content is <10 mg of water per litre of air (corresponding with a humidity of 50% at 23°C).

Table 4. Airway hyperresponsiveness (AHR) severity classification

PC_{20} mg·mL^{-1}	Interpretation
>16	Normal AHR
4.0–16.0	Borderline AHR
1.0–4.0	Mild AHR (positive test)
0.25–1.0	Moderate AHR
<0.25	Severe AHR

In many studies, a provocative concentration causing a 20% fall in forced expiratory volume in 1 second (PC_{20}) of <8 mg·mL^{-1} is taken as a positive result for the diagnosis of AHR. Reproduced from [32] with permission from the publisher.

Not all tests are suitable in the laboratory: for an appropriate test, the exercise should be vigorous from the start.

When assessing EIB, it is important to realise that negative results may be obtained when the wrong exercise challenge is chosen, when exercise tests start with a very low work-load, or when using the classic progressive exercise protocols for assessing maximum

Table 5. Direct and indirect airway challenge tests

	Type of stimulus	Methods	Standardised protocols/guidelines	[Ref.]
Direct tests	Histamine, methacholine or carbachol	Tidal breathing from nebuliser with 1.3 mL·minute^{-1} output	Doubling doses, administered for 2 minute at 5-minute intervals; FEV_1 assessed after each dose	[71]
		Dosimeter	9 uL per breath, 5 breaths per dose-doubling dose; FEV_1 assessed after each dose	[71]
		Yan method (handheld jet nebuliser)	Nine doses, 2.2–3.8 uL per squeeze	[79]
Indirect tests	Exercise with dry air	Bicycle or treadmill (vigorous exercise at >85% of max. heart rate)	Dry air at room temperature; inhalation at 60% of subject's MVV$^{\#}$ during 4–6 minutes; FEV_1 assessed at 1, 3, 5, 7, 10, 15 and 30 minutes after test; outcome variables are the maximal fall of FEV_1 ($\geqslant$10–15%) and AUC	[80]
	Eucapnic voluntary hyperpnoea	5% carbon dioxide, 21% oxygen, balance nitrogen		[81, 82]
	Hypertonic saline or distilled water challenge	Ultrasonic nebuliser, NaCl 4.5% or 0%	Flow $\geqslant$1.2 mL·minute^{-1}, exposure increases stepwise: 0.5, 1, 2, 4 and 8 minute (alternative: increases in NaCl concentration from 0.9% to 14.4%); FEV_1 assessed 60–90 seconds after each dose	[83]
	Dry powder mannitol challenge		Increasing doses (0, 5, 10, 20, 40, 80, 160, 160, 160 mg); FEV_1 assessed 1 minute after each dose	[84, 85]
	AMP challenge			[86]

AMP: adenosine monophosphate; FEV_1: forced expiratory volume in 1 second; MVV: maximal voluntary ventilation; AUC: area under the curve. $^{\#}$: $MVV = 35 \times FEV_1$.

working capacity. The greatest likelihood of identifying AHR based on exercise is achieved when the exercise intensity increases the ventilation and heart rate close to the desired level within 3 minutes of exercise. Because exercise challenge tests are relatively popular, two detailed protocols are summarised in table 6.

Table 6. Protocols for identifying exercise-induced bronchoconstriction in children

	Non-treadmill running	Treadmill running
Group	Children 6–11 years of age	Children 6–18 years of age
Measurement	FEV_1 at 3, 5 and 10 minutes and more if required FEV_1 pre-exercise >75% pred	FEV_1 pre- and post-exercise and at 5, 10, 15 and 30 minutes
Mode of exercise	Running on the flat at 7 km per hour	Walking then running on a treadmill at 4.1 km per hour on a 2.5% slope
Index of intensity	85–90% pred of maximum; heart rate 180–190 beats per minute	Heart rate 80–90% maximum; (220-age in years) beats per minute
Duration	6 minutes	8 minutes
Inspired air	Absolute water content <10 mg water per litre of air	Medical air: 20–30°C
Ventilation	*Via* mouth with nose-clip in place	Based on workload and oxygen consumption
Positive response	FEV_1 decrease >12% of baseline	FEV_1 decreases >10% of baseline

FEV_1: forced expiratory volume in 1 second; % pred: % predicted. Data taken from [57].

Feasibility, reproducibility and safety of AHR testing in (young) children

In schoolchildren and adolescents, the feasibility of AHR testing is very high and reproducibility is similar to that in adults [87], whereas in preschool children and infants, AHR testing is difficult, often not feasible and mainly used for research purposes [88, 89]. In adults and in children who can conduct spirometry reliably, routine pulse oximetry is not necessary as a safety measure [90], whereas in preschool children this might be recommended [91]. Several paediatric studies attempted to assess the differences between direct and indirect challenge tests and these demonstrated that direct or indirect tests could not discriminate between children with and without past or present wheeze, or the degree of clinical severity in this age group [91, 92]. For young children who cannot perform spirometric tests reproducibly or at all, it may be difficult to find reliable end-points. In one study, forced oscillation technique measurements were unreliable. Auscultation was highly insensitive and potentially dangerous because desaturations occurred in the absence of wheeze [91]; only transcutaneous oxygen saturation measurements seemed a suitable end-point [91], and this also proved to be quite reproducible [93]. In addition, the combination of tracheal/chest auscultation with arterial oxygen saturation monitoring seemed a suitable and safe end-point for direct tests in preschool children [94]. Further studies have explored additional functional end-points, such as the increase of diaphragmatic activity measurements with increasing dose of methacholine, and these seemed to correlate quite well with the decrease in FEV_1 in schoolchildren [95]. Standardisation or consensus statements for AHR testing in infants and preschool children are still lacking. AHR testing in this age group is currently not part of routine patient care and is mainly applied for research purposes.

Statement of Interest

None declared.

References

1. Sterk PJ, Bel EH. Bronchial hyperresponsiveness: the need for a distinction between hypersensitivity and excessive airway narrowing. *Eur Respir J* 1989; 2: 267–274.
2. Mark JD, McBride JT, Brooks JG, *et al.* Airway hyperreactivity and a history of clinical manifestations of asthma in childhood. *Pediatr Pulmonol* 1986; 2: 170–174.
3. Hargreave FE, Dolovich J, O'Byrne PM, *et al.* The origin of airway hyperresponsiveness. *J Allergy Clin Immunol* 1986; 78: 825–832.
4. Duiverman EJ, Den Boer JA, Roorda RJ, *et al.* Lung function and bronchial responsiveness measured by forced oscillometry after bronchopulmonary dysplasia. *Arch Dis Child* 1988; 63: 727–732.
5. Eber E, Zach MS. Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy). *Thorax* 2001; 56: 317–323.
6. Cropp GJ. Effectiveness of bronchodilators in cystic fibrosis. *Am J Med* 1996; 100: 19S–29S.
7. Koh YY, Lee MH, Kim CK, *et al.* A familial predisposition in bronchial hyperresponsiveness among patients with allergic rhinitis. *J Allergy Clin Immunol* 1998; 102: 921–926.
8. Choi SH, Yoo Y, Yu J, *et al.* Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. *Allergy* 2007; 62: 1051–1056.
9. Cuttitta G, Cibella F, La GS, *et al.* Non-specific bronchial hyper-responsiveness in children with allergic rhinitis: relationship with the atopic status. *Pediatr Allergy Immunol* 2003; 14: 458–463.
10. Hospers JJ, Postma DS, Rijcken B, *et al.* Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000; 356: 1313–1317.
11. Cook DG, Strachan DP. Health effects of passive smoking-10: summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999; 54: 357–366.
12. Postma DS, Bleecker ER, Amelung PJ, *et al.* Genetic susceptibility to asthma–bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995; 333: 894–900.
13. De Sanctis GT, Daheshia M, Daser A. Genetics of airway hyperresponsiveness. *J Allergy Clin Immunol* 2001; 108: 11–20.

14. Brusasco V. Airway structure to function relationships in asthma and COPD. *Monaldi Arch Chest Dis* 1997; 52: 597–599.
15. Laitinen LA, Elkin RB, Empey DW, *et al.* Bronchial hyperresponsiveness in normal subjects during attenuated influenza virus infection. *Am Rev Respir Dis* 1991; 143: 358–361.
16. Martinez FD, Antognoni G, Macri F, *et al.* Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am Rev Respir Dis* 1988; 138: 518–523.
17. Janssen NA, Brunekreef B, van Vliet P, *et al.* The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 2003; 111: 1512–1518.
18. Boezen HM, van der Zee SC, Postma DS, *et al.* Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. *Lancet* 1999; 353: 874–878.
19. Elliot J, Carroll N, Bosco M, *et al.* Increased airway responsiveness and decreased alveolar attachment points following *in utero* smoke exposure in the guinea pig. *Am J Respir Crit Care Med* 2001; 163: 140–144.
20. Bai TR, Knight DA. Structural changes in the airways in asthma: observations and consequences. *Clin Sci (Lond)* 2005; 108: 463–477.
21. Thibeault DW, Mabry SM, Ekekezie II, *et al.* Collagen scaffolding during development and its deformation with chronic lung disease. *Pediatrics* 2003; 111: 766–776.
22. Rolla G, Bucca C, Brussino L, *et al.* Reduction of bronchial responsiveness to methacholine after mitral valve replacement. *Respiration* 1991; 58: 81–84.
23. Rolla G, Bucca C, Caria E, *et al.* Bronchial responsiveness in patients with mitral valve disease. *Eur Respir J* 1990; 3: 127–131.
24. Moreno RH, Hogg JC, Pare PD. Mechanics of airway narrowing. *Am Rev Respir Dis* 1986; 133: 1171–1180.
25. Lambert RK. Analysis of bronchial mechanics and density dependence of maximal expiratory flow. *J Appl Physiol* 1986; 61: 138–149.
26. James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis* 1989; 139: 242–246.
27. Josephs LK, Gregg I, Holgate ST. Does non-specific bronchial responsiveness indicate the severity of asthma? *Eur Respir J* 1990; 3: 220–227.
28. Saetta M, Thiene G, Crescioli S, *et al.* Fatal asthma in a young patient with severe bronchial hyperresponsiveness but stable peak flow records. *Eur Respir J* 1989; 2: 1008–1012.
29. de Pee S, Timmers MC, Hermans J, *et al.* Comparison of maximal airway narrowing to methacholine between children and adults. *Eur Respir J* 1991; 4: 421–428.
30. Busse WW. The relationship of airway hyperresponsiveness and airway inflammation: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010; 138: Suppl. 2, 4S–10S.
31. Grol MH, Postma DS, Vonk JM, *et al.* Risk factors from childhood to adulthood for bronchial responsiveness at age 32–42 yr. *Am J Respir Crit Care Med* 1999; 160: 150–156.
32. Crapo RO, Casaburi R, Coates AL, *et al.* Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med* 2000; 161: 309–329.
33. Malo JL, Gauthier R, Lemire I, *et al.* Kinetics of the recovery of airway response caused by inhaled histamine. *Am Rev Respir Dis* 1985; 132: 848–852.
34. Gerritsen J, Koeter GH, Akkerboom HJ, *et al.* Recovery of FEV_1 after histamine challenge in asthmatic children. *Clin Allergy* 1987; 17: 119–126.
35. Merkus PJ, Rooda HM, van Essen-Zandvliet EE, *et al.* Assessment of bronchodilatation after spontaneous recovery from a histamine challenge in asthmatic children. *Thorax* 1992; 47: 355–359.
36. Burrows B. Allergy and the development of asthma and bronchial hyperresponsiveness. *Clin Exp Allergy* 1995; 25: Suppl. 2, 15–16.
37. Burrows B, Sears MR, Flannery EM, *et al.* Relation of the course of bronchial responsiveness from age 9 to age 15 to allergy. *Am J Respir Crit Care Med* 1995; 152: 1302–1308.
38. Van Asperen PP, Kemp AS, Mukhi A. Atopy in infancy predicts the severity of bronchial hyperresponsiveness in later childhood. *J Allergy Clin Immunol* 1990; 85: 790–795.
39. Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990; 85: 65–74.
40. Rijcken B, Schouten JP, Xu X, *et al.* Airway hyperresponsiveness to histamine associated with accelerated decline in FEV_1. *Am J Respir Crit Care Med* 1995; 151: 1377–1382.
41. van Schayck CP, Dompeling E, van Herwaarden CL, *et al.* Interacting effects of atopy and bronchial hyperresponsiveness on the annual decline in lung function and the exacerbation rate in asthma. *Am Rev Respir Dis* 1991; 144: 1297–1301.
42. Young S, Le Souef PN, Geelhoed GC, *et al.* The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991; 324: 1168–1173.
43. Hopp RJ, Townley RG, Biven RE, *et al.* The presence of airway reactivity before the development of asthma. *Am Rev Respir Dis* 1990; 141: 2–8.

44. Clough JB, Williams JD, Holgate ST. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough and wheeze. A 12-month longitudinal study. *Am Rev Respir Dis* 1991; 143: 755–760.
45. Brand PL, Duiverman EJ, Postma DS, *et al.* Peak flow variation in childhood asthma: relationship to symptoms, atopy, airways obstruction and hyperresponsiveness. Dutch CNSLD Study Group. *Eur Respir J* 1997; 10: 1242–1247.
46. Brand PL, Duiverman EJ, Waalkens HJ, *et al.* Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. *Thorax* 1999; 54: 103–107.
47. Rachiele A, Malo JL, Cartier A, *et al.* Circadian variations of airway response to histamine in asthmatic subjects. *Bull Eur Physiopathol Respir* 1983; 19: 465–469.
48. Sly PD, Landau LI. Diurnal variation in bronchial responsiveness in asthmatic children. *Pediatr Pulmonol* 1986; 2: 344–352.
49. Joos GF, O'Connor B, Anderson SD, *et al.* Indirect airway challenges. *Eur Respir J* 2003; 21: 1050–1068.
50. Sterk PJ. Airway hyperresponsiveness: using bronchial challenge tests in research and management of asthma. *J Aerosol Med* 2002; 15: 123–129.
51. Pattemore PK, Asher MI, Harrison AC, *et al.* The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. *Am Rev Respir Dis* 1990; 142: 549–554.
52. Kerrebijn KF, van Essen-Zandvliet EE, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987; 79: 653–659.
53. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, *et al.* Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992; 146: 547–554.
54. van den Berge M, Meijer RJ, Kerstjens HA, *et al.* PC(20) adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC(20) methacholine. *Am J Respir Crit Care Med* 2001; 163: 1546–1550.
55. Yoshikawa T, Shoji S, Fujii T, *et al.* Severity of exercise-induced bronchoconstriction is related to airway eosinophilic inflammation in patients with asthma. *Eur Respir J* 1998; 12: 879–884.
56. Lotvall J, Inman M, O'Byrne P. Measurement of airway hyperresponsiveness: new considerations. *Thorax* 1998; 53: 419–424.
57. Haby MM, Anderson SD, Peat JK, *et al.* An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. *Eur Respir J* 1994; 7: 43–49.
58. Anderson SD. Indirect challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010; 138: Suppl. 2, 25S–30S.
59. Joos GF. Do measures of bronchial responsiveness add information in diagnosis and monitoring of patients with asthma? *Eur Respir J* 2001; 18: 439–441.
60. Godfrey S, Springer C, Bar-Yishay E, *et al.* Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. *Eur Respir J* 1999; 14: 659–668.
61. Waalkens HJ, van Essen-Zandvliet EE, Hughes MD, *et al.* Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993; 148: 1252–1257.
62. Tamesis GP, Covar RA. Long-term effects of asthma medications in children. *Curr Opin Allergy Clin Immunol* 2008; 8: 163–167.
63. Hargreave FE, O'Byrne PM, Ramsdale EH. Mediators, airway responsiveness, and asthma. *J Allergy Clin Immunol* 1985; 76: 272–276.
64. Sont JK, Willems LN, Bel EH, *et al.* Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999; 159: 1043–1051.
65. Nuijsink M, Hop WC, Sterk PJ, *et al.* Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. *Eur Respir J* 2007; 30: 457–466.
66. Barben J, Riedler J. Measurement of bronchial responsiveness in children. *In:* Hammer J, Eber E, eds. Paediatric Pulmonary Function Testing. Basel, S. Karger AG, 2005; pp. 125–136.
67. Dautrebande L, Philippot E. Crise d'asthme experimentale par aerosols de carbaminoylcholine chez l'homme traitee par dispersat de phenylamino propane. Etude de l'action sur la respiration de ces substances par la determination du volume respiratoire utile [Experimental asthma by aerosols of carbaminoylcholine humans treated by dispersat of phenylamino propane. Study of the action on the respiration of these substances by the determination of useful respiratory volume]. *Presse Med* 1941; 49: 942–946.
68. Cockcroft DW, Killian DN, Mellon JJ, *et al.* Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7: 235–243.
69. Hargreave FE, Ryan G, Thomson NC, *et al.* Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J Allergy Clin Immunol* 1981; 68: 347–355.

70. Guidelines for standardization of bronchial challenges with (nonspecific) bronchoconstricting agents. *Bull Eur Physiopathol Respir* 1983; 19: 495–514.
71. Sterk PJ, Fabbri LM, Quanjer PH. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests. European Community for Steel and Coal. *Eur Respir J* 1993; 6: Suppl. 16, 53–83.
72. Kongerud J, Soyseth V, Johansen B. Room temperature influences output from the Wright jet nebulizer. *Eur Respir J* 1989; 2: 681–684.
73. Chan KN, Clay MM, Silverman M. Output characteristics of DeVilbiss No. 40 hand-held jet nebulizers. *Eur Respir J* 1990; 3: 1197–1201.
74. Merkus PJ, van Essen-Zandvliet EE, Parlevliet E, *et al.* Changes of nebulizer output over the years. *Eur Respir J* 1992; 5: 488–491.
75. Ryan G, Dolovich MB, Obminski G, *et al.* Standardization of inhalation provocation tests: influence of nebulizer output, particle size, and method of inhalation. *J Allergy Clin Immunol* 1981; 67: 156–161.
76. Malmberg P, Larsson K, Sundblad BM, *et al.* Importance of the time interval between FEV1 measurements in a methacholine provocation test. *Eur Respir J* 1993; 6: 680–686.
77. Birnie D, thoe Schwartzenberg GW, Hop WC, *et al.* Does the outcome of the tidal breathing and dosimeter methods of assessing bronchial responsiveness in children with asthma depend on age? *Thorax* 1990; 45: 199–202.
78. Chinn S. Methodology of bronchial responsiveness. *Thorax* 1998; 53: 984–988.
79. Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983; 38: 760–765.
80. Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972; 47: 882–889.
81. Anderson SD, Argyros GJ, Magnussen H, *et al.* Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *Br J Sports Med* 2001; 35: 344–347.
82. Rundell KW, Anderson SD, Spiering BA, *et al.* Field exercise *vs* laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. *Chest* 2004; 125: 909–915.
83. Smith CM, Anderson SD. Hyperosmolarity as the stimulus to asthma induced by hyperventilation? *J Allergy Clin Immunol* 1986; 77: 729–736.
84. Brannan JD, Anderson SD, Perry CP, *et al.* The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005; 6: 144.
85. Anderson SD, Charlton B, Weiler JM, *et al.* Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; 10: 4.
86. Avital A, Springer C, Bar-Yishay E, *et al.* Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. *Thorax* 1995; 50: 511–516.
87. Malmberg LP, Nikander K, Pelkonen AS, *et al.* Acceptability, reproducibility, and sensitivity of forced expiratory volumes and peak expiratory flow during bronchial challenge testing in asthmatic children. *Chest* 2001; 120: 1843–1849.
88. Stick SM, Turner DJ, Le Souef PN. Lung function and bronchial challenges in infants: repeatability of histamine and comparison with methacholine challenges. *Pediatr Pulmonol* 1993; 16: 177–183.
89. Delacourt C, Benoist MR, Waernessyckle S, *et al.* Repeatability of lung function tests during methacholine challenge in wheezy infants. *Thorax* 1998; 53: 933–938.
90. Cockcroft DW, Hurst TS, Marciniuk DD, *et al.* Routine pulse oximetry during methacholine challenges is unnecessary for safety. *Chest* 2000; 118: 1378–1381.
91. Wilson NM, Bridge P, Phagoo SB, *et al.* The measurement of methacholine responsiveness in 5 year old children: three methods compared. *Eur Respir J* 1995; 8: 364–370.
92. Wilson NM, Bridge P, Silverman M. Bronchial responsiveness and symptoms in 5–6 year old children: a comparison of a direct and indirect challenge. *Thorax* 1995; 50: 339–345.
93. Phagoo SB, Wilson NM, Silverman M. Repeatability of methacholine challenge in asthmatic children measured by change in transcutaneous oxygen tension. *Thorax* 1992; 47: 804–808.
94. Yong SC, Smith CM, Wach R, *et al.* Methacholine challenge in preschool children: methacholine-induced wheeze *versus* transcutaneous oximetry. *Eur Respir J* 1999; 14: 1175–1178.
95. Sprikkelman AB, Van Eykern LA, Lourens MS, *et al.* Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. *J Appl Physiol* 1998; 84: 897–901.

Chapter 15

Treatment of acute asthma

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SUMMARY: Shortness of breath, cough, wheezing and/or chest tightness are the classical symptoms of acute asthma with its underlying pathophysiological mechanisms of bronchoconstriction, airway inflammation and airway hypersecretion. Therefore, the logical treatment for acute asthma is to act against the pathophysiological mechanisms of asthma using a supportive treatment to reduce respiratory distress caused by these pathophysiological mechanisms.

The classical medical treatment for acute asthma consists of inhaled bronchodilators and inhaled or systemic steroids. Supportive therapy is performed by supplying additional oxygen and/or, if necessary, adding ventilator support, either noninvasive or invasive.

According to the severity of acute asthma, acute episodes can be either treated by one single measure, such as an increased use of short-acting bronchodilators or a combination of additional measures, such as the additional use of inhaled steroids. In severe cases, repetitive measures and the use of systemic treatment as well as ventilatory support and consequently hospital admission may be necessary.

KEYWORDS: Acute asthma, bronchodilator, childhood asthma, noninvasive ventilation, steroids

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Despite modern and efficient anti-inflammatory drugs being available in most countries to control asthma, it is still one of the most prevalent chronic diseases in childhood and asthmatic children still frequently present with acute exacerbations to the emergency room [1]. There are some well-known risk factors that increase the frequency of acute exacerbations [2]. If asthmatic children present with an acute exacerbation, it is pertinent to consider other differential diagnoses in order to introduce an appropriate treatment for these children [3]. In addition, the initial assessment has to address the severity of the exacerbation, again to initiate the adequate therapy options [4]. Once assessed, asthmatic children receive their treatment [5]. Shortness of breath, cough, wheezing and/or chest tightness are the classical symptoms of acute asthma with its underlying pathophysiological mechanisms of bronchoconstriction, airway inflammation and airway hypersecretion. Therefore, the logical treatment for acute asthma is to act against the pathophysiological mechanisms using supportive treatment to reduce respiratory distress caused by these pathophysiological mechanisms. The classical medical treatment for acute asthma consists

of inhaled bronchodilators and inhaled or systemic steroids. Despite there being pathophysiological evidence of viscous secretion playing an important role in acute asthma, there are no well-designed studies looking at the efficiency of anti-mucoid treatment in this clinical situation in children [6]. Supportive therapy is performed by supplying additional oxygen and/or, if necessary, adding ventilator support, either noninvasive or invasive. According to the severity of acute asthma, acute episodes can be either treated by one single measure, such as the use of short-acting bronchodilators, or by a combination of additional measures, such as the additional use of inhaled steroids. In severe cases, repetitive measures and the use of systemic treatment as well as ventilatory support and consequently hospital admission may be necessary. To avoid further exacerbations educational measures are important [7].

Risk factors for severe acute asthma

There are different potential risk factors discussed in the literature, however, not always with consistent findings. Despite these sometimes controversial findings and the lack of clear-cut predictive parameters, some general statements can be made and are of importance regarding the response to treatment and its prognosis. These factors can be defined in relation to hospital admissions in general and to intensive care admissions in particular. It has been shown by KELLER *et al.* [8] that children with a severe grade of asthma, a lack of private insurance, or of female sex are at an increased risk of requiring management in the intensive care unit (ICU). However, the authors also stated, that all severities of asthma may require intensive care admission. In this study it was interestingly noted that age, race, month of admission, household smoking exposure and a positive family history of atopy places a child at no greater risk for intensive care admission. This finding is in contrast to other studies, which show an increased risk of near fatal asthma (which is defined as the occurrence of respiratory arrest and/or coma necessitating emergency tracheal intubation and mechanical ventilation) and fatal asthma for Black race, male sex and season. Asthma mortality among Black subjects has consistently been higher than that for White subjects, with the death rate from asthma being about twice as high [9]. In contrast to race not being a predictive factor for intensive care admission, KELLER *et al.* [8] showed that the rate of regular hospital admissions among non-Caucasians increased [8]. In younger children, males are generally known to have an increased incidence and mortality from asthma [10, 11] but this changes at puberty. Recent European data showed different seasonal patterns for hospitalisation due to acute asthma and asthma mortality. Whereas there is an increased hospitalisation rate in autumn and winter, more children die of asthma between June and August [12–16]. There are several socioeconomic factors which are associated with the increased incidence of severe asthma, such as exposure to tobacco smoke, low-income and lack of third-party insurance [17–20]. Whereas early reports noted that only those children with severe, chronic asthma were vulnerable to mortality due to asthma and that the risk of death from asthma among children with mild, episodic asthma was remote, retrospective surveys indicate that 15–30% of asthma deaths ($<$0.1% of patients with asthma) occur in patients whose disease is categorised as only mild asthma and that most of these patients have a worsening of asthma symptoms for a 2–7-day period prior to presenting to the emergency room [21, 22]. Risk factors for death due to asthma vary between the different age groups. Whereas hospitalisation for asthma in the 6 months preceding death and deterioration in the previous month are major risk factors in children aged 1–4 years, non-adherence to asthma treatment and previous life-threatening episodes and deterioration in the previous month are more important risk factors in older children. A factor found in most children with fatal asthma is a delay in seeking medical help [14]. Whereas older studies showed that excess use of short-acting β-agonists is a risk factor for near fatal or fatal asthma, a more recent report suggest that patterns of use are a marker for more severe asthma rather than cause of severe attacks [23]. In addition, the chronic use of long-acting β-agonists in patients with asthma has been associated with a small increased risk of asthma-related death [24].

Differential diagnosis

The differential diagnosis of acute respiratory symptoms is pertinent for providing adequate and immediate treatment. Supplemental oxygen and inhaled bronchodilators are the usual measures taken by emergency medical services, which may be an adequate treatment in most of the potential diagnoses mimicking asthma [25]. It has been shown that misdiagnosis is present in up to 30% of outpatients, in 1% of general admissions and 10% of intensive care admissions [26]. According to the history and clinical examination the following differential diagnosis of obstructive airways disease has to be considered (table 1). In the emergency room, the physician bases his diagnosis frequently on a previous diagnosis of asthma, which may be justified if the child has had a history of lower airway obstruction that has responded to inhaled bronchodilators or if the child has had a positive bronchial provocation test. However, a diagnosis has always to be verified by a careful medical history and clinical examination and other differential diagnoses have to be excluded in this way, as the initial diagnosis is pertinent for the appropriate treatment.

Assessment

Primarily, patients presenting in the emergency room can be identified based on historical information according to their risk factors for fatal or near fatal asthma. Relevant findings from history taking are the severity of previous exacerbations, the types and doses of medications taken and comorbidities [27].

In addition, and most importantly, patients have to be assessed and categorised regarding the severity of their actual asthma exacerbation. This is performed by a subjective clinical assessment in combination with some additional objective measurements. However, numerous studies have shown that even experienced clinicians are not very good at quantifying the degree of airflow obstruction by auscultation.

Table 1. Differential diagnosis based on history and presentation

Clinical signs	Possible differential diagnoses
History	
Symptoms since birth	Cystic fibrosis, CLD of prematurity, primary ciliary dyskinesia, airway/lung malformation, gastro-oesophageal reflux
Family history of uncommon airway problems	Cystic fibrosis, CLD, neuromuscular disease, airway/lung malformation
Acute occurrence without pre-existing problems	Foreign body aspiration
Symptoms	
Fever, upper airway symptoms	Acute airway tract infection (bronchitis, bronchiolitis, pneumonia)
Vomiting with cough, dysphagia	Gastro-oesophageal reflux, aspiration
Abnormal voice or hoarseness	Laryngeal or vocal cord problem
Inspiratory and/or expiratory stridor	Laryngitis, tracheitis, laryngo- or tracheomalacia, vascular malformation
Failure to thrive	Cystic fibrosis, CLD, immune deficiency, airway/lung malformation, gastro-oesophageal reflux
Predominantly symptoms during sleep	Upper airway disease (post nasal drip), gastro-oesophageal reflux
Radiological signs	
Focal or persistent radiological changes	Airway/lung malformation, gastro-oesophageal reflux with signs of aspiration, foreign body aspiration, bronchiectasis

CLD: chronic lung disease.

Clinical assessment

The initial assessment of the patient provides pertinent information [22]. The most important measures of the prevention of an imminent acute respiratory decompensation are to achieve adequate oxygen supply to the vital organs. Therefore, first, hypoxaemia needs to be treated; secondly, sufficient cardiovascular function achieved; and thirdly, alveolar function needs to be improved.

The first alterations in vital signs such as blood pressure, pulse rate and/or respiratory rate are indications for immediate and more aggressive treatment. Low blood pressure and bradycardia indicate immediate resuscitative intervention with exclusions of underlying complications of acute asthma attacks, such as pneumothorax and pneumomediastinum. The clinical signs related to a severe asthma attack or impending respiratory arrest, which may necessitate mechanical ventilation, are shown in table 1. Signs that ventilatory support may be needed are clinically persistent respiratory distress, despite conventional intervention, and low or normal arterial carbon dioxide tension (P_{a,CO_2}) despite hypoxia, as a sign of persistent hyperventilation with potential fatigue. Signs of imminent respiratory decompensation are significant breathing fatigue, progressive acidosis in blood gas analysis, haemodynamic instability and reduction of alertness. Auscultation of the chest is helpful in addressing the quality and quantity of airway obstruction and ventilation.

Objective measurements

Blood gases

More than 30 years ago it was shown that blood gases and acid-base balance are helpful in evaluating the severity and the treatment response in asthmatic children [28]. 10 years later, the same has been shown for transcutaneous blood gas analysis [29, 30]. In those days, the technique had obvious advantages over other physiological measures in that the technique was noninvasive and did not demand active cooperation from the child. Furthermore, such an investigation does not require sedation of the child. Since these early stages of blood gas analysis in the assessment of an asthma attack in children, it has gained a primordial role in evaluating a child with asthma and has a firm place in all asthma guidelines [31–33]. Pulse oximetry is widely used to guide the physicians in the evaluation of the severity and the treatment responses. Values below 90% in room air are generally believed to indicate severe exacerbation. However, most patients entering the emergency department are given immediate supplemental oxygen and therefore, oxygen is usually assessed under additional oxygen. It is important to note that the measurement of oxygen saturation alone is not sufficient to monitor a child with a severe acute asthma exacerbation (AAE) and signs of further deterioration. The assessment of carbon dioxide is crucial in the evaluation and guidance of clinical decisions. As noninvasive measures of carbon dioxide tension (P_{CO_2}) are not widely available, arterial blood gas analysis is normally used to detect children at risk for respiratory failure and hence, likely to need additional ventilator support. In addition, an arterial blood gas analysis is usually considered if there is incongruity between subjective and objective evaluation.

Pulmonary function

As clinical evaluation of an asthma attack, in general, and of airway obstruction, in particular, is not always easy, it has become a standard technique to assess the degree of severity by obtaining peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1) measures by forced exhalation, the advantage of this approach being objectivity. Lung function measurements can be useful not only for the objective assessment of the degree of airway obstruction, hence the severity of the asthma attack, but also for detecting alternative diagnoses. A normal or near normal lung function measurement excludes a significant asthma exacerbation. There is some evidence that lung function measures such as PEF measurements can be useful in predicting short-term outcome in patients with acute asthma after initiation of treatment. However, despite being

recommended in most guidelines, including Global Initiative for Asthma (GINA) guidelines [32] and the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR3) [33], there is some controversy on the clinical usefulness of lung function measurements in the assessment of acute asthma. In a recent study it has been shown that in children between the ages of 6 and 17 years who presented to an urban free-standing children's hospital emergency department and who were assessed with portable spirometry and a clinical asthma score, only 35% were able to successfully perform portable spirometry, and that successful spirometry attempts were associated with older age, lower respiratory rates, lower heart rates and lower clinical asthma score. In other words, increasing asthma severity correlated with a decreased likelihood of successfully obtaining a useful FEV1 measurement. The authors showed that compared with cases of mild asthma, a patient with moderate asthma is 33% less likely to be able to perform spirometry, and a patient with severe asthma 93% less likely to perform spirometry. In addition, they have shown that the clinical asthma scoring system demonstrated poor correlation with portable spirometry measurements in terms of severity classification [34]. These findings are explained by the fact that measurements of forced expiration used in the assessment of bronchospasm depend on effort and require significant cooperation by the patient. This effort and cooperation are progressively more limited in the younger patient and when the severity of the asthma exacerbation intensifies. Despite the limited usefulness of spirometry in general and peak flow measurements in particular; they are still widely used in the ambulatory setting [35]. Peak flow meter measurements are not highly reproducible and can be unreliable predictors of asthma exacerbations [36, 37]. The most recent study concluded that utilising portable spirometry as a severity measure in the acute asthmatic patient for clinical or research purposes is difficult and problematic, a statement that the authors would like to underline. Despite their limited use, PEF or FEV1 measures still have their place in modern asthma guidelines [31] (table 2).

Assessment scores

As stated previously, the assessment of asthma is difficult in children because, on one hand, the clinical evaluation is not always easy and, on the other hand, the objective measure of forced expiration is often impractical. Whereas some assessment scores, such as the National Asthma Council Guidelines (NACG), use clinical and forced expiratory measures in combination and group children with acute exacerbation into mild, moderate, and severe life-threatening categories based on several examination findings and the measurements of PEF and FEV1, other scores are purely clinical [31, 38]. One of these, the pulmonary index score (PIS) (table 3), a composite objective clinical observation that composes a score from 0 to 12, has recently been validated against the NACG score (table 4) [31, 38]. This score, which has been used previously and been shown to be a valuable research tool has the advantage of being objective and easy to derive [39–42]. The authors have been able to show that the PIS correlates well with the NACG score, with significant differences in median PIS values across different NACG score severity categories. In addition, they showed that a PIS of six or greater predicts with high sensitivity (85%) and specificity (75%) moderate and

Table 2. Clinical assessment

Signs of a severe asthma attack in an older child
Severe agitation
Hunched sitting position with arms supporting torso (tripod)
Limited ability to speak
Use of accessory muscles
Respiratory rate >30 breaths·min^{-1}
Signs of a severe asthma attack in an infant
Use of accessory muscles
Supraclavicular and intercostal retractions
Nasal flaring
Paradoxical breathing
Cyanosis
Respiratory rate >60 breaths·min^{-1}
Signs of impending respiratory arrest
Lethargy or confusion
Silent chest
Paradoxical thoracoabdominal movement
Bradycardia

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Table 3. Pulmonary Index Score (PIS)

Score	PIS components			
	Respiratory rate beats·min^{-1}	Wheezing	Inspiratory:expiratory ratio	Accessory muscle use
0	<30	None	5:2	0
1	31–45	Terminal expiration with stethoscope	5:3–5:4	+/-
2	46–60	Entire expiration with stethoscope	1:1	+/+
3	>60	Audible without stethoscope or silent chest	<1:1	+++

+/-: questionable increase; +/+: apparent increase; +++: maximal increase.

severe asthma, whereas a PIS of eight or greater predicts severe asthma, again with a relatively high sensitivity (88%) and specificity (77%). The authors concluded that the PIS can be applied as a useful clinical tool for the assessment and monitoring of asthma in children in the emergency department. The Paediatric Asthma Severity Score (PASS) was essentially derived from the PIS and could be interpreted as a simplified version of the PIS. The PASS consists of three clinical items including the severity of wheeze, the respiratory work and the prolongation of expiration (ratio of the length of expiration over inspiration). Individual items are scored from 0 (none/mild) to 2 (severe) and the PASS score is the sum of all components. In the original publication the PASS was able to discriminate between those patients who did and did not require hospitalisation, with area under the receiver operating characteristic curve of 0.82 [43]. The Preschool Respiratory Assessment Measure (PRAM) assesses the following items: suprasternal retractions, scalene muscle contraction, air entry, wheezing and oxygen saturation with individual scores between 0 and 3 [44]. The score predicts hospital admission with an area under the receiver operating characteristic curve of 0.69 [45]. Recently, the PRAM has been found to be valuable also in schoolchildren [46].

The RAD score comprises three routinely measured bedside clinical parameters: respiratory rate, accessory muscle use and decreased breath sounds, and has criterion validity comparable to the PRAM and the PASS score due to its simplicity and as it is specifically suited for bedside use [47].

Treatment

The treatment of acute asthma consists of the application of inhaled bronchodilators and inhaled or systemic steroids. Hypersecretion is an important pathophysiological problem in acute asthma

Table 4. National Asthma Council Guidelines (NACG) assessment of acute asthma in children (2006)

Symptoms	NACG asthma severity category		
	Mild	Moderate	Severe/life-threatening
Altered consciousness	No	No	Agitated/confused/drowsy
Pulse oximetry on presentation %	>94	90–94	<90
Speech	Sentences	Phrases	Words/unable to speak
Pulse beats·minute^{-1}	<100	100–200	>200
Central cyanosis	Absent	Absent	Present
Wheeze intensity	Variable	Moderate	Quiet
PEFR % pred	>60	40–60	<40/unable to perform
FEV$_1$ % pred	>60	40–60	<40/unable to perform

PEFR: peak expiratory flow rate; % pred: % predicted; FEV$_1$: forced expiratory volume in 1 second. Reproduced and modified from [38] with permission from the publisher.

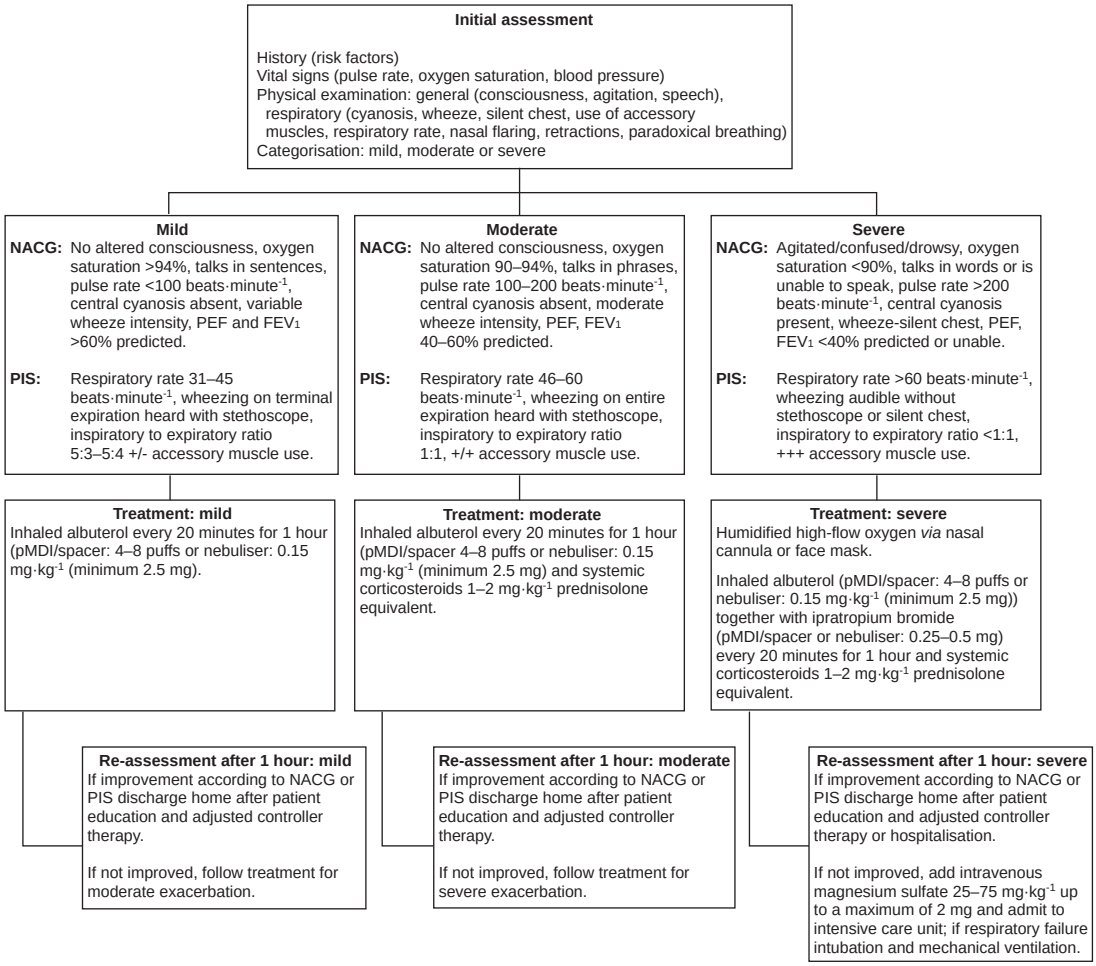
Initial assessment
History (risk factors)
Vital signs (pulse rate, oxygen saturation, blood pressure)
Physical examination: general (consciousness, agitation, speech), respiratory (cyanosis, wheeze, silent chest, use of accessory muscles, respiratory rate, nasal flaring, retractions, paradoxical breathing)
Categorisation: mild, moderate or severe
Mild
NACG: No altered consciousness, oxygen saturation >94%, talks in sentences, pulse rate <100 beats·minute-1, central cyanosis absent, variable wheeze intensity, PEF and FEV1 >60% predicted.
PIS: Respiratory rate 31–45 beats·minute-1, wheezing on terminal expiration heard with stethoscope, inspiratory to expiratory ratio 5:3–5:4 +/- accessory muscle use.
Moderate
NACG: No altered consciousness, oxygen saturation 90–94%, talks in phrases, pulse rate 100–200 beats·minute-1, central cyanosis absent, moderate wheeze intensity, PEF, FEV1 40–60% predicted.
PIS: Respiratory rate 46–60 beats·minute-1, wheezing on entire expiration heard with stethoscope, inspiratory to expiratory ratio 1:1, +/+ accessory muscle use.
Severe
NACG: Agitated/confused/drowsy, oxygen saturation <90%, talks in words or is unable to speak, pulse rate >200 beats·minute-1, central cyanosis present, wheeze-silent chest, PEF, FEV1 <40% predicted or unable.
PIS: Respiratory rate >60 beats·minute-1, wheezing audible without stethoscope or silent chest, inspiratory to expiratory ratio <1:1, +++ accessory muscle use.
Treatment: mild
Inhaled albuterol every 20 minutes for 1 hour (pMDI/spacer: 4–8 puffs or nebuliser: 0.15 mg·kg-1 (minimum 2.5 mg).
Treatment: moderate
Inhaled albuterol every 20 minutes for 1 hour (pMDI/spacer 4–8 puffs or nebuliser: 0.15 mg·kg-1 (minimum 2.5 mg) and systemic corticosteroids 1–2 mg·kg-1 prednisolone equivalent.
Treatment: severe
Humidified high-flow oxygen via nasal cannula or face mask.
Inhaled albuterol (pMDI/spacer: 4–8 puffs or nebuliser: 0.15 mg·kg-1 (minimum 2.5 mg)) together with ipratropium bromide (pMDI/spacer or nebuliser: 0.25–0.5 mg) every 20 minutes for 1 hour and systemic corticosteroids 1–2 mg·kg-1 prednisolone equivalent.
Re-assessment after 1 hour: mild
If improvement according to NACG or PIS discharge home after patient education and adjusted controller therapy.
If not improved, follow treatment for moderate exacerbation.
Re-assessment after 1 hour: moderate
If improvement according to NACG or PIS discharge home after patient education and adjusted controller therapy.
If not improved, follow treatment for severe exacerbation.
Re-assessment after 1 hour: severe
If improvement according to NACG or PIS discharge home after patient education and adjusted controller therapy or hospitalisation.
If not improved, add intravenous magnesium sulfate 25–75 mg·kg-1 up to a maximum of 2 mg and admit to intensive care unit; if respiratory failure intubation and mechanical ventilation.

Figure 1. Management of asthma exacerbations in children in the emergency department. PEF: peak expiratory flow; FEV1: forced expiratory volume in 1 second; PIS: pulmonary index score; NACG: National Asthma Council Guidelines; pMDI: pressurised metered-dose inhaler. +/-: questionable increase; +/+: apparent increase; +++: maximal increase.

leading to further bronchial obstruction. However, there are no well-designed studies looking at the efficiency of mucoactive medications in this specific clinical situation in children and the available data does not provide evidence that anti-mucoid treatment is effective [48, 49]. Additional oxygen is an important first-line supportive therapy in children with hypoxaemia. In the case of imminent respiratory decompensation, ventilator support, either noninvasive or invasive, has to be added. The classification of AAE into mild, moderate and severe exacerbation allows the treatment to be adapted accordingly (fig. 1).

Mild and moderate exacerbations

In mild asthma exacerbations, which are mainly managed at home, one single measure, classically the use of a short-acting bronchodilator, typically albuterol (alternative name salbutamol), is sufficient (fig. 1).

There is some discussion in the literature on the value of racemic albuterol, the β_2-receptor agonists most widely used *versus* levalbuterol. Racemic albuterol is a 1:1 racemic mixture of the (R)-enantiomer responsible for the bronchodilatatory effect and the (S)-enantiomer. The (S)-enantiomer has a 10-fold slower rate of metabolism and there has been some concern that it can

accumulate in patient's plasma and lung tissue with frequent dosing. In addition, it has been suggested that (S)-albuterol can stimulate eosinophil recruitment and hence, have pro-inflammatory effects and can lead to bronchial hyperresponsiveness (BHR) and/or bronchoconstriction. Levalbuterol contains only the (R)-enantiomer that demonstrates 100-fold more potent β_2-receptor binding compared to the (S)-enantiomer. Due to the absence of the negative side-effects of (S)-albuterol it has been claimed to have better efficacy in the acute situation [50]. At the doses used, in a recent study, racemic albuterol appeared to be superior to levalbuterol with respect to changes in FEV1 and asthma score. However, hospital admissions were numerically higher in the racemic albuterol group. A finding which is supported by another study showing reduced hospital admissions with levalbuterol [51]. However, if the literature is reviewed as a whole, there is no clear advantage of one over the other [52–54]. Some of the differences seen in responses to bronchodilators in children with acute asthma may be explained by a β_2-adrenoceptor polymorphism [55]. Inhaled terbutaline sulfate is comparable to albuterol in treating acute bronchoconstriction. One study compared the efficacy of terbutaline sulfate delivered by Turbuhaler dry powder inhaler (AstraZeneca, Lund, Sweden) or pressurised metered-dose inhaler (pMDI) with spacer in children presenting with acute asthma showing no significant differences in clinical benefit or side-effects [56]. Formoterol is a fast-acting, long-acting β_2-agonist indicated for long-term asthma treatment. Several studies demonstrated the efficacy and safety of formoterol as a rescue-treatment for acute asthma symptoms. In children with mild-to-moderate asthma exacerbation formoterol seems to be as effective as terbutaline. However, there are no studies in severe acute asthma and therefore formoterol should not be used in this case [57].

In children, inhaled medication should be administered by either using a nebuliser or a pMDI with a holding chamber. It has been shown that both modalities are effective in delivering inhaled bronchodilators and that there is no difference in the clinical efficacy regarding the following outcomes: rate of hospital admission, length of time spent in the emergency department or PEF [58]. Therefore, the choice of drug delivery depends upon cooperation and the ability to use a device and other factors such as, the possibility to give supplemental oxygen during nebulisation in the case of hypoxia in hospitalised children and in the emergency department, or to mix various drug solutions, rather than a difference in outcome [59, 60]. Therefore, nebulisation is strongly recommended in children with significant agitation, respiratory distress and in young children. The doses of albuterol usually administered are either 5–10 puffs of the pMDI (100 μg per puff) or 0.15 $mg \cdot kg^{-1}$ (minimum dose 2.5 mg) of the solution, repeated every 20 minutes as needed for 1 hour.

Children with a mild asthma exacerbation who do not respond to bronchodilators and who continue to present with cough, wheeze and/or shortness of breath despite inhaled albuterol, and children with a moderate asthma exacerbation should be monitored and receive additional oxygen and, in addition to inhaled albuterol, systemic and oral corticosteroids (fig. 1). Supplemental oxygen is delivered by nasal cannula or mask with the aim to maintain oxygen saturation above 92%. Early treatment with systemic corticosteroids results in decreased duration and severity of an acute asthma episode and systemic steroids have been shown to speed the resolution of bronchial obstruction, to improve symptom scores, to improve quality of life, to decrease the rate of hospital admission and to decrease the rate of relapse and β-agonist use after discharge [61–63]. The reason may be that while systemic corticosteroids are traditionally thought to exert their anti-inflammatory effect over hours, they may also increase the effectiveness of fast-acting β_2-agonists [64, 65]. Oral route of administration and intravenous route of administration have both shown equal efficacy [33]. However, in general, oral administration is the preferred route if there are no contra-indications such as swallowing problems, nausea or vomiting. The dose usually recommended in guidelines is 1–2 $mg \cdot kg^{-1}$ prednisone equivalent in a palatable form (prednisolone, dexamethasone, betamethasone) in one dose with possible repetition after 6 hours with unclear evidence of its additional benefit [66, 67]. However, while the use of systemic corticosteroids in adults and older children is supported by data, the situation is different in young preschool children with acute wheezing associated with viral infection. In a large study in preschool children aged 10–60 months presenting with mild-to-moderate wheezing a 5-day course

of oral prednisolone was not superior to placebo in regard to duration of hospitalisation, PRAM scores, the total dose of inhaled albuterol or side-effects [68].

Whereas systemic corticosteroids are widely recommended and used, the use of inhaled corticosteroids (ICS) in AAE remains controversial. The potential benefits of ICS for the treatment of AAE include direct delivery to the airways and reduced systemic exposure. Several studies failed to note any positive effects of ICS in the acute setting [69–72]. However, the two studies of SCHUH and co-workers [69, 72] included only children who presented to the emergency department with very severe asthma and FEV1 less than 60% [69] or 50–79% predicted [72]. Therefore, the benefit of inhaled steroids may greatly depend on the severity of the AAE. The other studies claimed that the acute use of ICS provides only modest benefit in the control of asthma attack in children [70] and that a combination of inhaled β_2-agonist and corticosteroids yields better results than ICS alone [71]. Two evidence-based reviews reported good results for repeated high doses given in the initial phase of the exacerbation [73, 74]. It is apparently the high dose that is the key factor for clinical success, reaching up to five times the recommended amount [75]. A more recent study has shown that AAE in young children can be effectively controlled at home with the use of high repetitive doses of inhaled budesonide or inhaled fluticasone, initially together with β_2-agonists, given at the beginning of the attack, for a period of 4–8 days [76]. Despite this promising data, systemic steroids remain the first choice, as its administration is easy and economical. Children with mild and moderate exacerbations have to be followed up closely. If there is insufficient improvement or deterioration, treatment has to be adapted according to the algorithm proposed in figure 1. Reasons for hospitalisation are lack of improvement within 1–4 hours despite adequate repeated doses of inhaled betamimetics and systemic corticosteroids, oxygen saturation persistently below 92% and patients with a history of bad asthma control and recurrent exacerbations. An important additional reason for hospitalisation may be the lack of a sufficient social and familiar network to guarantee adequate monitoring and treatment.

Severe exacerbation

In severe exacerbations, one single measure is not sufficient and an approach with a combination of several measures is needed. It is pertinent to treat these patients in a room equipped for resuscitation procedures in order to carefully and continuously monitor cardiac rhythm, pulse oximetry, blood pressure and if available carbon dioxide and to take, if necessary, the measures to manage respiratory failure and haemodynamic instability. Correction of hypoxaemia by using supplemental oxygen is pertinent. Humidified high-flow oxygen either *via* nasal cannula or *via* face mask should be applied with a constant flow-rate of 4–5 $L \cdot min^{-1}$. Nasal obstruction with consecutive mouth breathing should be taken into consideration when using nasal cannula. Flows have to be $\geqslant 4$ $L \cdot min^{-1}$ when using a face mask to prevent re-breathing. Oxygen with a flow-rate of 6–8 $L \cdot min^{-1}$ should be used as the driving force for nebulisation in children with severe hypoxaemia. Usually, the standard treatment for severe exacerbations consists again of inhaled bronchodilators and systemic steroids followed by additional measures taken according to the initial evaluation and the course of the asthma episode. Usually the initial dose and frequency of inhaled bronchodilators are the same as in mild and moderate exacerbations. However, for severe exacerbations with significant respiratory distress, bronchodilators should be delivered by continuous nebulisation. It has been shown that continuous nebulisation resulted in greater improvement in lung function parameters, lower hospitalisation rate and no difference in side-effects [77]. Prompt initiation of systemic corticosteroids is pertinent in the management of severe exacerbations at the same dose and the same route of administration as in mild exacerbations unresponsive to bronchodilators alone, or in moderate exacerbations.

Ipratropium bromide is an acetylcholine antagonist that acts on the bronchial smooth muscle. Although parasympathetic fibres are only present in the large airways, ipratropium can have a generalised action throughout the lung. However, the β-adrenergic receptors are distributed more peripherally, creating an ideal situation for combined action [78]. The bronchodilator effect of ipratropium is somewhat slower than that of the β_2-agonists, but combined administration can

potentiate the effects of both drugs. Although the administration of repeated doses of ipratropium is generally recommended in the first 24–48 hours, the optimal dose and frequency in children with asthma crises has still not been established [33, 79]. In a recent study, six nebulised inhalations, which is a slightly larger number than has been used in other studies, have been administered and have shown an improvement in clinical parameters (asthma score), in oxygen saturation and in lung function parameters, and a reduction in hospital admission in children who were stratified according to the severity of their asthma exacerbation [80]. In only three other studies, which analysed the effect of albuterol plus ipratropium, were patients stratified according to clinical severity of the asthma [81–83]. In all these studies, the clinical and functional improvement with the combination of albuterol and ipratropium was greater in severe asthma crises than in moderate crises. This finding underlines the importance of an early initial treatment with albuterol plus ipratropium in children with more severe asthma crises. Commonly, ipratropium at a dose of 0.25–0.5 mg is mixed with albuterol for nebulisation in the same nebuliser at the same frequency of administration (every 20 minutes for 1 hour and then according to a re-evaluation). Alternatively, ipratropium bromide can be used alone or in combination with albuterol as a pMDI with a holding chamber. In children, the dose is 4–48 puffs every 20 minutes for 1 hour and then according to a re-evaluation.

Intravenous magnesium sulfate is an efficient adjunctive therapy in children whose response is suboptimal and in those who have deteriorated. The drug causes relaxation of the bronchial smooth muscle by inhibiting calcium influx into smooth muscle cells and also has anti-inflammatory effects. Systematic reviews of the available literature have shown that intravenous magnesium sulfate significantly improves lung function and reduces hospitalisation rate, with the greatest benefits seen in asthmatics with more severe exacerbations [84–86]. In children, the recommended dose is 25–75 $mg \cdot kg^{-1}$ up to a maximum of 2 mg. The intravenous route is an effective and economical route of administration, whereas the effects of the inhaled route of administration are less clear.

Heliox is a mixture of helium and oxygen (ratio 80:20 or 70:30) and has a lower density than ambient air. As it causes less turbulent gas flow, mainly in the large airways, it has the potential to reduce work of breathing and improve dyspnoea [33, 87]. GUPTA and CHEIFETZ [88] reviewed the administration of heliox in the paediatric ICU and concluded that despite several studies showing significant improvements in children with severe asthma, it is difficult to form definitive conclusions due to the heterogeneity and small sample studies. Early application of heliox may be of some benefit for selected patients with severe exacerbation and may even prevent intubation in some of the patients.

A recent randomised, placebo-controlled trial investigated the effect of a heliox driven albuterol nebulisation in children with moderate-to-severe status asthmaticus. They found no significant benefits on duration of hospitalisation and stay on the ICU or clinical improvements according to the clinical asthma score [89].

There is some additional but sparse evidence for other treatments, such as parenteral β-agonists, methylxanthines, leukotriene receptor antagonists and ketamine. The conclusion of a meta-analysis was that evidence is lacking to support the use of intravenous β-agonists in patients with severe asthma in the emergency department, except possibly for those patients for whom inhaled therapy is not feasible [90]. Similar recommendations are drawn from another meta-analysis for the adjunctive therapy with aminophylline, where no difference could be shown in lung function or hospital admission rate, however, more side-effects of the treatment, such as arrhythmia and vomiting were found [91]. Leukotriene receptor antagonists either administered by the oral or the intravenous route have shown improvements in lung function, but not in clinical outcomes, without any side-effects [92, 93]. Ketamine, a rapid acting anaesthetic that acts to relax bronchial smooth muscle by a direct effect on smooth muscle and indirectly by stimulating the release of catecholamines and by inhibiting vagal tone, has not been shown to have a clinical effect in children with asthma exacerbation [94]. The use of noninvasive ventilation in asthmatic patients is not well established despite the potential benefits of such a treatment, and some evidence that has

shown improvements in lung function parameters, hospital admission rates and decreased bronchodilator use [95, 96]. Noninvasive positive pressure ventilation (NPPV) is delivered either as continuous positive airway pressure (CPAP) or varying between higher inspiratory and lower expiratory pressures (bilevel positive airway pressure; BiPAP). The prerequisites for the application of NPPV are as follows: 1) the child is awake and cooperative; 2) oxygen transport is sufficient; 3) circulation is stable; 4) few secretions within the upper airways; 5) no vomiting; and 6) no air leak syndrome. Expiratory pressure may be set at 5 cmH_2O and inspiratory pressure between 5–10 cmH_2O and further adapted according to oxygenation and ventilation [97]. One important problem is the interface, as it can be challenging to find a tightly fitting mask in this small sized population [5]. If all these measures are not successful and children with severe asthma exacerbation show signs of respiratory failure, intubation and mechanical ventilation can be life-saving and should be performed quickly and safely in the appropriate setting [22]. Indications for intubation and mechanical ventilation are as follows: 1) lack of improvement with NPPV; 2) apnoea or respiratory arrest; 3) progressive central cyanosis despite supplemental oxygen; 4) $P_{a,CO_2} \geqslant 65$ mmHg; and 5) drowsiness or confusion, or coma. In order to reduce agitation, decrease intrinsic airway pressure and improve gas exchange, sedatives and neuromuscular blockade are important measures in children requiring intubation and mechanical ventilation. Ketamine, a dissociative anaesthetic has been shown to be useful as an induction agent for intubation as it may diminish the bronchoconstrictor response. It is normally given by an intravenous bolus of 2 mg·kg body weight^{-1}, followed by continuous infusion of 20–60 μg·kg body weight^{-1}·min^{-1}. Alternatives are morphine and midazolam. If necessary, muscle relaxation may be induced using vecuronium in single doses or as continuous infusion [5]. From the literature there is no clear agreement on the ventilation mode. While volume-control preset has been recommended, there is more and more experience using pressure-control modes. Most patients benefit from positive end-expiratory pressure between 4–5 cmH_2O [98]. Inspiratory and expiratory times are set by visual control of the chest excursions and the flow–time curve (complete inspiration and expiration without abortion of the flow-curve). The peak inspiratory pressure is set according to the gas-exchange. In severe cases, permissive ventilation with controlled hypoventilation (arterial oxygen saturation (S_{a,O_2}) 80–90%, high P_{a,CO_2} accepted as long as pH >7.2) may prevent barotrauma [99].

Follow-up

Children treated in an emergency department because of an AAE have a high morbidity shortly after discharge. This morbidity is associated with the need for rescue medication and school absenteeism due to symptom persistence [100]. Improvement of asthma control by maintenance of treatment with ICS at adequate doses and regular follow-up improve the short-term outcome. [101, 102] Such preventive measures are likely to be more effective by the use of written action plans.

A recent study by DUCHARME *et al.* [103] showed that the provision of a written action plan led to better patient adherence to both maintenance inhaled corticosteroid use and medical follow-up. The use of a written action plan has also been associated with a reduction in emergency department visits and hospitalisations [104]; however, such written action plans remain underused despite being recommended in most guidelines for asthma management [105].

Another measure that has been shown to improve the short-term outcome is telephone coaching, which may be especially indicated for children living in urban regions [106].

Most hospitalisations and emergency department visits are avoidable with adequate asthma management, including early diagnosis and asthma education [107]. Up to two-thirds of children hospitalised with acute asthma had been poorly controlled during the previous year, frequently under treated and claimed to be insufficiently educated [108].

The recognition and, as a consequence, the avoidance of known asthma triggers, including passive and active smoking are essential measures for the follow-up of children after AAE [109].

Comorbid allergic rhinitis is associated with a higher risk of asthma attacks; hence control of allergic rhinitis has the potential to reduce asthma-related hospitalisations [110]. A risk factor for an ICU admission in children with asthma is a history of multiple emergency visits in the past year [111] and such children should be referred to a paediatric respiratory specialist in order to be properly assessed and educated; *vice versa*, admission to ICU is a predictor of hospital readmission. Children requiring artificial ventilation are at an elevated risk of mortality in the subsequent years and therefore require a close follow-up [112].

Asthma outreach programmes have been shown to be of particular use for children at high risk of asthma attacks [113]. The effects of educational interventions aiming to educate parents and children for better understanding of the basic problems of asthma and the consequences of allergy, asthma treatment and symptom perception and to improve self-assessment and management, have been studied extensively [114]. Asthma school programmes have been shown to increase not only theoretical knowledge and self-perception of asthma control but also compliance with treatment and inhalation technique [114, 115]. A recent review analysed 38 studies, including a total of 7,843 children. The risk of subsequent emergency department visits and hospital admissions was significantly reduced following educational interventions delivered to children and parents. In addition, unscheduled doctor visits were reduced. Interestingly, other outcomes such as pulmonary function tests, rescue medication use and quality of life did not seem to be affected [116]. An older review of 26 randomised controlled trials and six clinical trials revealed improvement of lung function and in the measures of self-efficacy, fewer days of school absences and less emergency visits [117].

In conclusion, children with frequent AAE and asthma-related hospitalisations (*i.e.* those with ICU admission) should be closely followed up and educational interventions, such as asthma schools should be applied. Careful assessments for comorbidity, differential diagnoses and inhalation technique are pertinent in the prevention of further asthma exacerbations.

Statement of Interest

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References

1. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol* 2008; 122: 662–668.
2. Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy* 2009; 39: 193–202.
3. Hedlin G, Bush A, Lødrup Carlsen K, *et al.* Problematic severe asthma in children, not one problem but many: a GA^{2}LEN initiative. *Eur Respir J* 2010; 36: 196–201.
4. Øymar K, Halvorsen T. Emergency presentation and management of acute severe asthma in children. *Scand J Trauma Resusc Emerg Med* 2009; 17: 40–51.
5. Schramm CM, Carro CL. Advances in treating acute asthma exacerbations in children. *Curr Opin Pediatr* 2009; 21: 326–332.
6. Rogers DF, Barnes PJ. Treatment of airway mucus hypersecretion. *Ann Med* 2006; 38: 116–125.
7. Brown MD, Reeves MJ, Meyerson K, *et al.* Randomized trial of a comprehensive asthma education program after an emergency department visit. *Ann Allergy Asthma Immunol* 2006; 97: 44–51.
8. Keller K, Sran S, Laszlo D, *et al.* Asthma management in children: factors identifying patients at risk for intensive care unit treatment. *J Asthma* 1994; 31: 393–400.
9. National Center for Health Statistics: Annual Summary of Births, Marriages, Divorces, and Deaths. Monthly Vital Statistics Report. U.S. Public Health Service. Hyattsville, MD, 2008. www.cdc.gov/nchs/products/mvsr.htm
10. Evans R, Mullally DI, Wilson RW. National trends in the morbidity of asthma in the U.S. *Chest* 1987; 91: Suppl. 6, 65S–74S.
11. Sly RM. Mortality from asthma in children 1979–1984. *Ann Allergy* 1988; 60: 433–443.
12. Weiss KB. Seasonal trends in US asthma hospitalisations and mortality. *JAMA* 1990; 263: 2323–2328.
13. Anagnostou K, Harrison B, Iles R, *et al.* Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001–2006. *Prim Care Respir J* 2012; [Epub ahead of print DOI: 10.4104/pcrj.2011.00097].

14. Jørgensen IM, Jensen VB, Bülow S, *et al.* Asthma mortality in the Danish child population: risk factors and causes of asthma death. *Pediatr Pulmonol* 2003; 36: 142–147.
15. Watson L, Turk F, James P, *et al.* Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med* 2007; 101: 1659–1664.
16. Campbell MJ, Holgate ST, Johnston SL. Trends in asthma mortality. Data on seasonality of deaths due to asthma were omitted from paper but editorial's author did not know. *BMJ* 1997; 315: 1012.
17. Weitzman M, Gortmaker S, Walker DK, *et al.* Maternal smoking and childhood asthma. *Pediatrics* 1990; 85: 505–511.
18. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89: 21–26.
19. Schwartz J, Gold D, Dockery DW, *et al.* Predictors of asthma and persistent wheeze in a national sample of children in the United States. *Annu Rev Respir Dis* 1990; 142: 555–562.
20. Grumach AS, Carneiro-Campaio MM, Lima JL, *et al.* The growth curve in asthmatic children. *Allergol Immunopathol* 1985; 13: 221–228.
21. Mellis CM, Phelan PD. Asthma deaths in children – a continuing problem. *Thorax* 1977; 32: 29–34.
22. Adams JY, Sutter ME, Albertson TE. The patient with asthma in the emergency department. *Clinic Rev Allergy Immunol* 2011; [Epub ahead of print DOI: 10.1007/s12016-011-8273-z].
23. Rea HH, Garrett JE, Lanes SF, *et al.* The association between asthma drugs and severe life threatening attacks. *Chest* 1996; 110: 1446–1451.
24. Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists – the influence of values. *N Engl J Med* 2009; 360: 1592–1595.
25. Sapien RE, Lapidus J, Coors L, *et al.* Prehospital EMS treatment of pediatric asthma and what happens before help arrives? *J Asthma* 1997; 34: 477–481.
26. Lazarus SC. Clinical practice. Emergency treatment of asthma. *N Engl J Med* 2010; 363: 755–764.
27. Turner MO, Noertjojo K, Vedal S, *et al.* Risk factors for near fatal asthma. A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998; 157: 1804–1809.
28. Oberger E, Engstrom I. Blood gases and acid-base balance in children with bronchial asthma. *Lung* 1978; 155: 111–122.
29. Wennergren G, Engstrom I, Bjure J. Transcutaneous oxygen and carbon dioxide levels and a clinical symptom scale for monitoring the acute asthmatic state in infants and young children. *Acta Paediatr Scand* 1986; 75: 465–469.
30. Wennergren G, Holmgren D, Engstrom I, *et al.* Using transcutaneous blood gases to evaluate treatment effects on acute asthma in young children. *Scand J Clin Lab Invest* 1988; 48: Suppl. 189, 41–44.
31. National Asthma Council Australia. Asthma Management Handbook. 6th Edn. Melbourne, National Asthma council Australia Ltd, 2006.
32. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention: NHLBI/WHO Workshop Report, 2005. Publication No 02-3659.
33. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma – summary report 2007. *J Allergy Clin Immunol* 2007; 120: Suppl. 5, S94–S138.
34. Schneider WV, Bulloch B, Wilkinson M, *et al.* Utility of portable spirometry in a pediatric emergency department in children with acute exacerbation of asthma. *J Asthma* 2011; 48: 248–252.
35. Wildhaber J, Hammer J. Asthma and wheezing disorders. *Eur Respir Monogr* 2010; 47: 209–224.
36. Eid N, Yandell B, Howell L. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000; 105: 354–358.
37. Mortimer KM, Redline S, Kattan M. Are peak flow and symptom measures good predictors of asthma hospitalizations and unscheduled visits? *Pediatr Pulmonol* 2001; 31: 190–197.
38. Hsu P, Lam LT, Browne G. The pulmonary index score as a clinical assessment tool for acute childhood asthma. *Ann Allergy Asthma Immunol* 2010; 105: 425–429.
39. Pierson WE, Bierman CW, Stamm SJ, *et al.* Double-blind trial of aminophylline in status asthmaticus. *Pediatrics* 1971; 48: 642–646.
40. Barnett PL, Caputo GL, Baskin M, *et al.* Intravenous *versus* oral corticosteroids in the management of acute asthma in children. *Ann Emerg Med* 1997; 29: 212–217.
41. Scarfone RJ, Loiselle JM, Joffe MD, *et al.* A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000; 36: 572–578.
42. Becker AB, Nelson NA, Simons FE. The pulmonary index: assessment of a clinical score for asthma. *Am J Dis child* 1984; 138: 574–576.
43. Gorelick MH, Stevens MW, Schultz TR, *et al.* Performance of a novel clinical score, the pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med* 2004; 11: 10–18.
44. Chalut DS, Ducharme FM, Davis GM. The Pre-school Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. *J Pediatr* 2000; 137: 762–768.
45. Gouin S, Robidas I, Gravel J, *et al.* Prospective evaluation of two clinical scores for acute asthma in children 18 months to 7 years of age. *Acad Emerg Med* 2010; 17: 598–603.

46. Ducharme FM, Chalut D, Plotnick L, *et al.* The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr* 2008; 152: 476–480.
47. Arnold DH, Gebretsadik T, Abramo TJ, *et al.* The RAD score: a simple acute asthma severity score compares favorably to more complex scores. *Ann Allergy Asthma Immunol* 2011; 107: 22–28.
48. Balsamo R, Lanata L, Egan CG. Mucoactive drugs. *Eur Respir Rev* 2010; 19: 127–133.
49. Rogers DF. Mucoactive agents for airway mucus hypersecretory diseases. *Respir Care* 2007; 52: 1176–1193.
50. Wilkinson M, Bulloch B, Garcia-Filion P, *et al.* Efficacy of racemic albuterol *versus* levalbuterol used as a continuous nebulization for the treatment of acute asthma exacerbations: a randomized, double-blind, clinical trial. *J Asthma* 2010; 48: 188–193.
51. Carl JC, Myers TR, Kirchner HL, *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. *J Pediatr* 2003; 143: 731–736.
52. Hardasmalani MD, DeBari V, Bithoney WG, *et al.* Levalbuterol *versus* racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; 21: 415–419.
53. Qureshi F, Zaritsky A, Welch C, *et al.* Clinical efficacy of racemic albuterol *versus* levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; 46: 29–36.
54. Andrews T, McGintee E, Mittal MK, *et al.* High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial. *J Pediatr* 2009; 155: 205–210.
55. Martin AC, Zhang G, Rueter K, *et al.* β2-adrenoceptor polymorphisms predict response to β2-agonists in children with acute asthma. *J Asthma* 2008; 45: 383–388.
56. Drblik S, Lapierre G, Thivierge R, *et al.* Comparative efficacy of terbutaline sulphate delivered by Turbuhaler dry powder inhaler or pressurised metered dose inhaler with Nebuhaler spacer in children during an acute asthmatic episode. *Arch Dis Child* 2003; 88: 319–323.
57. Bussamra MH, Stelmach R, Rodrigues JC, *et al.* A randomized, comparative study of formoterol and terbutaline dry powder inhalers in the treatment of mild to moderate asthma exacerbations in the pediatric acute care setting. *Ann Allergy Asthma Immunol* 2009; 103: 248–253.
58. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) *versus* nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006; 2: CD000052.
59. Brand PL. Key issues in inhalation therapy in children. *Curr Med Res Opin* 2005; 21: S27–S32.
60. Laube BL, Janssens HM, de Jongh FH, *et al.* What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011; 37: 1308–1331.
61. Rowe BH, Edmonds ML, Spooner CH, *et al.* Corticosteroid therapy for acute asthma. *Respir Med* 2004; 98: 275–284.
62. Rowe BH, Spooner C, Ducharme FM, *et al.* Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001; 1: CD002178.
63. Rowe BH, Spooner C, Ducharme FM, *et al.* Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2000; 2: CD000195.
64. Taylor IK, Shaw RJ. The mechanism of action of corticosteroids in asthma. *Respir Med* 1993; 87: 261–277.
65. Svedmyr N. Action of corticosteroids on beta-adrenergic receptors. Clinical aspects. *Am Rev Respir Dis* 1990; 141: S31–S38.
66. Emerman CL, Cydulka RK. A randomised comparison of 100mg *vs* 500 mg dose of methylprednisolone in the treatment of acute asthma. *Chest* 1995; 107: 1559–1563.
67. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* 2001; 1: CD001740.
68. Panickar J, Lakhanpaul M, Lambert PC, *et al.* Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009; 360: 329–338.
69. Schuh S, Reisman J, Alshehri M, *et al.* A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000; 343: 689–694.
70. Gibson PG, Powell H. Initial corticosteroid therapy for asthma. *Curr Opin Pulm Med* 2006; 12: 48–53.
71. Hendeles L, Sherman J. Are inhaled corticosteroids effective for acute exacerbations of asthma in children? *J Pediatr* 2003; 142: Suppl. 2, S26–S33.
72. Schuh S, Dick PT, Stephens D, *et al.* High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma. *Pediatrics* 2006; 118: 644–650.
73. Volovitz B. Inhaled budesonide in the management of acute worsenings and exacerbations of asthma: a review of the evidence. *Respir Med* 2007; 101: 685–695.
74. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. *Chest* 2006; 130: 1301–1311.
75. Volovitz B, Nussinovitch M. Management of children with severe asthma exacerbation in the emergency department. *Paediatr Drugs* 2002; 4: 141–148.
76. Volovitz B, Bilavsky E, Nussinovitch M. Effectiveness of high repeated doses of inhaled budesonide or fluticasone in controlling acute asthma exacerbations in young children. *J Asthma* 2008; 45: 561–567.
77. Camargo CA Jr, Spooner CH, Rowe BH. Continuous *versus* intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003; 4: CD001115.

78. Partridge M, Saunders K. Site of action of ipratropium bromide and clinical and physiological determinants of response in patients with asthma. *Thorax* 1981; 36: 530–533.
79. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. A national clinical guideline. May 2008 (revised January 2012).
80. Iramain R, Lopez-Herce J, Coronel J, *et al.* Inhaled salbutamol plus ipratropium in moderate and severe asthma crises in children. *J Asthma* 2011; 48: 298–303.
81. Zorc JJ, Pusic MV, Ogborn CJ, *et al.* Ipratropium bromide added to asthma treatment in the pediatric emergency department. *Pediatrics* 1999; 103: 748–752.
82. Benito Fernández J, Maintegui Raso S, Sánchez Echanitz J, *et al.* Eficacia de la administración precoz de bromuro de ipratropio nebulizado en niños con crisis asmática. [Efficacy of early administration of nebulized ipratropium bromide in children with asthmatic crisis.] *An Esp Pediatr* 2000; 53: 217–222.
83. Sienra Monje JJL, Bermejo Guevara MA, del Rio Navarro BE, *et al.* Grado y duración de la broncodilatación mediante la administración de un agonista b2 solo vs un agonista b2 mas bromuro de ipratropio en niños con asma aguda. [Degree and duration of bronchodilatation with an agonist beta 2 administered alone *versus* an agonist beta 2 administered with ipratropium bromide in children with acute asthma.] *Rev Alergia México* 2000; 47: 26–29.
84. Mohammed S, Goodcare S. Intravenous and nebulised magnesium sulphate for acute asthma: a systematic review and meta-analysis. *Emerg Med J* 2007; 24: 823–830.
85. Rowe BH, Camargo CA Jr. The role of magnesium sulfate in the acute and chronic management of asthma. *Curr Opin Pulm Med* 2008; 14: 70–76.
86. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005; 90: 74–77.
87. Rodrigo G, Pollack C, Rodrigo C, *et al.* Heliox for non intubated acute asthma patients. *Cochrane Database Syst Rev* 2006; 4: CD002884.
88. Gupta VK, Cheifetz IM. Heliox administration in the pediatric intensive care unit: an evidence-based review. *Pediatr Crit Care Med* 2005; 6: 204–211.
89. Bigham MT, Jacobs BR, Monaco MA, *et al.* Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: a randomized, placebo-controlled trial. *Pediatr Crit Care Med* 2010; 11: 356–361.
90. Travers AH, Rowe BH, Barker S, *et al.* The effectiveness of *iv* beta-agonists in treating patients with acute asthma in the emergency department: a meta-analysis. *Chest* 2002; 122: 1200–1207.
91. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. *Cochrane Database Syst Rev* 2000; 4: CD002742.
92. Camargo CA Jr, Gurner DM, Smithline HA, *et al.* A randomised placebo-controlled study of intravenous montelukast for the treatment of acute asthma. *J Allergy Clin Immunol* 2010; 125: 374–380.
93. Ramsay CF, Pearson D, Mildenhall S, *et al.* Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax* 2010; 66: 7–11.
94. Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Ann Emerg Med* 2005; 46: 43–50.
95. Soroksky A, Stav D, Shpirer I. A pilot prospective randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003; 123: 1018–1025.
96. Gupta D, Nath A, Agarwal R, *et al.* A prospective randomised controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. *Respir Care* 2010; 55: 536–543.
97. Mayordomo-Colunga J, Medina A, Rey C, *et al.* Non-invasive ventilation in pediatric status asthmaticus: a prospective observational study. *Pediatr Pulmonol* 2011; 46: 949–955.
98. Bohn D, Kissoon N. Acute asthma. *Pediatr Crit Care Med* 2001; 2: 151–163.
99. Wang XF, Hong JG. Management of severe asthma exacerbation in children. *World J Pediatr* 2011; 7: 293–301.
100. Benito-Fernandez J, Onis-Gonzalez E, Alvarez-Pitti J, *et al.* Factors associated with short-term clinical outcomes after acute treatment of asthma in a pediatric emergency department. *Pediatr Pulmonol* 2004; 38: 123–128.
101. Javier Benito-Fernandez. Short-term clinical outcomes of acute treatment of childhood asthma. *Curr Opin Allergy Clin Immunol* 2005; 5: 241–246.
102. Kallstrom TJ. Evidence-based asthma management. *Respir Care* 2004; 49: 783–792.
103. Ducharme FM, Zemek RL, Chalut D, *et al.* Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med* 2011; 183: 195–203.
104. Lieu TA, Quesenberry CP Jr, Capra AM, *et al.* Outpatient management practices associated with reduced risk of pediatric asthma hospitalization and emergency department visits. *Pediatrics* 1997; 100: 334–341.
105. Self TH, Chrisman CR, Jacobs AR, *et al.* Preventing emergency department visits and hospitalizations for asthma by use of oral corticosteroids at home: are we adhering to national guidelines? *J Asthma* 2010; 47: 1123–1127.
106. Smith SR, Jaffe DM, Fisher EB Jr, *et al.* Improving follow-up for children with asthma after an acute emergency Ddpartment visit. *J Pediatr* 2004; 145: 772–777.
107. Coffman JM, Cabana MD, Halpin HA, *et al.* Effects of asthma education on children's use of acute care services: a meta-analysis. *Pediatrics* 2008; 121: 575–586.

108. Fuhrman C, Dubus JC, Marguet C, *et al.* Hospitalizations for asthma in children are linked to undertreatment and insufficient asthma education. *J Asthma* 2011; 48: 565–571.
109. Flores G, Abreu M, Tomany-Korman S, *et al.* Keeping children with asthma out of hospitals: parents' and physicians' perspectives on how pediatric asthma hospitalizations can be prevented. *Pediatrics* 2005; 116: 957–965.
110. Thomas M. Allergic rhinitis: evidence for impact on asthma. *BMC Pulm Med* 2006; 6: Suppl. 1, S4.
111. Belessis Y, Dixon S, Thomsen A, *et al.* Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol* 2004; 37: 201–209.
112. Triasih R, Duke T, Robertson CF. Outcomes following admission to intensive care for asthma. *Arch Dis Child* 2011; 96: 729–734.
113. Greineder DK, Loane KC, Parks P. A randomized controlled trial of a pediatric asthma outreach program. *J Allergy Clin Immunol* 1999; 103: 436–440.
114. Guevara JP, Wolf FM, Grum CM, *et al.* Effects of educational interventions for self management of asthma in children and adolescents: systematic review and metaanalysis. *BMJ* 2003; 326: 1308–1309.
115. Živković Z, Radić S, Cerović S, *et al.* Asthma School Program in children and their parents. *World J Pediatr* 2008; 4: 267–273.
116. Boyd M, Lasserson TJ, McKean MC, *et al.* Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database of Syst Rev* 2009; 2: CD001290.
117. Wolf FM, Guevara JP, Grum CM, *et al.* Educational interventions for asthma in children. *Cochrane Database Syst Rev* 2003; 1: CD000326.

Chapter 16

Treatment of infant and preschool asthma

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SUMMARY: Many infants and preschool children have asthmatic symptoms with wheezing, triggered predominantly by colds. However, the pathogenesis of wheezing in this age group is heterogeneous.

The heterogeneity of asthma in infants and preschool children is reflected by the varied effectiveness of the medication.

Children with signs of atopy and who also wheeze between colds respond positively to inhaled corticosteroids (ICS), while the effects of ICS are often unsatisfactory in viral wheeze. Periodic treatment with ICS or montelukast has been shown to reduce symptoms, to some degree, in preschool wheezers with intermittent wheezing in conjunction with viral infections. However, the available data indicate that the treatment effect in episodic viral wheeze is, at best, modest.

Randomised controlled trials in preschool children have not shown that early steroid treatment has a disease-modifying effect and early steroid treatment does not appear to reduce the prevalence of asthma at school age.

KEYWORDS: Asthma, child, infant, preschool, treatment, wheeze

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Many infants and young children have asthmatic symptoms with wheezing, usually in association with colds [1, 2]. However, wheezing in the young child is heterogeneous. The majority of these infants, and many preschool children, have "viral wheeze" [3, 4]. As a rule, these children show no signs of allergy, and wheeze mainly only when they have colds. This is sometimes called "episodic viral wheeze" [5]. The pathogenetic mechanisms of episodic viral wheeze are not fully established, but are probably different to those of eosinophil inflammation. Most children with viral wheeze grow out of their wheeze at 2–3 years of age, but some continue to wheeze in connection with colds up to school age [5].

In children with eczema or allergic sensitisation, the symptoms triggered by colds can be regarded as virus-induced asthma exacerbations. Children who also have symptoms between colds, sometimes called multiple-trigger wheeze, are more prone to developing "true" asthma [5]. The differences in terms of inflammatory markers between episodic viral wheeze and multiple-trigger wheeze have recently been reported, supporting the more allergic nature of multiple-trigger wheeze [6]. However, it should be recognised that viral wheeze and multiple-trigger wheeze are

not sharply delineated entities [7]. For example, a child may have only virally induced symptoms initially but then may develop allergic symptoms. Furthermore, it should be acknowledged that viral infections are also the most common cause of acute asthma symptoms in children who have asthma and allergic sensitisation.

The high percentage of infants and young children with wheeze and asthmatic symptoms demonstrates that there is a real need for effective treatment. However, the treatment effect is often modest or unsatisfactory in this young age group. The treatment effect in viral wheeze is generally not as good as in ''true'' asthma.

Non-pharmacological measures

Tobacco smoke

There is strong evidence to suggest that exposure to environmental tobacco smoke can both induce infant and preschool wheeze, and lead to exacerbations [8, 9]. The effects of early smoke exposure may persist into the late teens [10, 11]. Maternal smoking during pregnancy appears to be most harmful, but parental smoking at home during infancy is also harmful. Furthermore, children who grow up in a smoking environment are more likely to become smokers themselves [11]. For this reason, parents who smoke should be encouraged to stop.

Breastfeeding

Many studies show that breastfeeding reduces the risk of wheezing disorder during the first year of life [2, 12, 13]. The effect has been shown to persist up to 4 years of age, especially in the case of episodic viral wheeze [14, 15]. However, there is no convincing evidence to suggest that breastfeeding prevents the development of allergic asthma or allergic sensitisation [13].

Furry pets

If a child with asthma is sensitised to furry pets, exposure to them will impair asthma. Consequently, this kind of allergen exposure should be avoided. However, if the child is not sensitised, current studies do not support the hypothesis that the exposure is harmful, especially if the child has viral wheeze and no signs of atopy. In contrast, several studies have found that children who grow up with pets are less likely to develop allergic sensitisation to pets [16, 17]. Even if this has been ascribed, at least in part, to selection bias [18], *i.e.* many atopic families do not have furry pets, available data do not support the view that children growing up with dogs and cats develop more sensitisation.

Parental education

Parental knowledge of the child's asthma and how best to manage the disease is often insufficient. Parental education has been shown to improve adherence, asthma control in the child and the quality of life of the family [19]. Easy-to-understand information about asthma and what influences it should be provided. The importance of adherence should be stressed. Parents should also be taught the correct inhalation technique and how to handle exacerbations [20].

Pharmacological treatment

Relief medication

Short-acting β_2-agonists

The drugs of choice for acute symptoms of wheeze in infants and preschool children are inhaled short-acting β_2-agonists, such as salbutamol or terbutaline. It is sometimes said that β_2-agonists

do not work in infancy. Nonetheless, it has been convincingly demonstrated that infants actually have functioning β_2-receptors that are able to produce bronchodilation [21–24]. However, it should be recognised that paradoxical responses to β_2-agonists have been described in infants [25].

Inhaled administration is preferred as it provides rapid symptom relief, while systemic side-effects in terms of tachycardia and tremor are minimised, although oral administration has the same bronchodilatory effects. The intravenous infusion of salbutamol or terbutaline can be indicated in severe acute asthma.

Long-acting β_2-agonists

Both salmeterol and formoterol have bronchodilatory and bronchoprotective effects in preschool children [26, 27]. For maintenance treatment, long-acting β_2-agonists should be used in combination with inhaled corticosteroids (ICS).

In schoolchildren, beneficial additive effects have been shown through the combination of ICS and long-acting β_2-agonists [28, 29]. In preschool children there are retrospective data indicating that treatment with ICS in combination with a long-acting β_2-agonist is efficacious and safe [30]. However, we lack double-blind, randomised, placebo-controlled studies of the addition of long-acting β_2-agonists to ICS in preschool children.

Control medication

Inhaled corticosteroids

Systematic reviews convincingly demonstrate that infants and preschool children with asthma who receive ICS have less wheezing and asthma exacerbations, and improved symptoms and lung function [31, 32]. Similarly, preschool children with asthma symptoms and a positive Asthma Predictive Index (API) generally respond positively to maintenance treatment with ICS [33, 34].

Several clinical scores have been developed for selecting preschool children with a greater risk of asthma. The API is used for children who experience three episodes of wheezing before 3 years of age. It includes two major (parental history of asthma or personal history of eczema) and three minor (blood eosinophilia, wheezing without colds and allergic rhinitis) criteria. The presence of one major or two minor criteria is associated with an increased risk of continued wheezing at 5 years of age [35]. In a modified API, allergic sensitisation to at least one aeroallergen has been added to the major criteria, and allergic sensitisation to milk or peanut replaces allergic rhinitis as a minor criterion [36].

In contrast with the positive effects of ICS in preschool children with positive API, the effects on recurrent viral wheeze are often unsatisfactory. Some studies have demonstrated a modest reduction in symptom severity with periodic treatment with high-dose inhaled or nebulised corticosteroids in intermittent viral wheeze [37, 38]. Other studies have found no reduction in wheezing episodes with continuous ICS treatment [39].

Local side-effects of treatment with ICS, such as thrush or hoarseness, are rare in infants and preschool children [40]. The systematic review by KADITIS *et al.* [31] concludes that deceleration in linear growth rate is the most frequent systemic adverse effect of maintenance treatment with ICS. Some studies report a slight reduction in linear growth [34], while other studies find no significant impairment [41].

Does early ICS treatment alter the natural course of asthma?

Randomised controlled trials in preschool children have been unable to show that early steroid treatment has a disease-modifying effect [34, 42–44]. Asthma symptoms returned when ICS therapy was discontinued and the prevalence of asthma at school age was not reduced.

Leukotriene receptor agonists

The leukotriene receptor agonist that is approved for treatment in young children is montelukast (from 6 months of age). Montelukast is available as granules or tablets. The dose is 4 mg once daily.

Montelukast has been shown to reduce bronchial hyperresponsiveness in (BHR) preschool children, tested with hyperventilation with cold dry air or metacholine [45, 46].

In 2–5-year-old children with persistent asthma, montelukast improved asthma symptoms and reduced exacerbations by 30% [47]. Maintenance treatment with montelukast reduced the number of asthma episodes by one third in 2–5-year-old children with intermittent asthma [48]. In a subgroup analysis of children aged 2–5 years, periodic treatment with montelukast, started in connection with asthma symptoms or the first signs of a cold, significantly reduced unscheduled healthcare visits. However, there was no significant effect on hospitalisations, duration of episodes or courses of oral steroids [49].

In overall terms, compared with inhaled nebulised corticosteroids, montelukast appears to be less effective in reducing exacerbations in children with mild persistent asthma [50].

No effect was seen on wheeze or cough following hospitalisation for bronchiolitis/wheezing bronchitis induced by respiratory syncytial virus (RSV) [51].

It has been concluded that there are no safety problems when it comes to the use of montelukast in young children [20].

Sodium cromoglycate

Sodium cromoglycate (cromolyn) was widely used as control therapy in children with asthma in the 1970s and 1980s. Today, it has been replaced by the use of ICS or montelukast. Moreover, a Cochrane review has concluded that sodium cromoglycate has no beneficial effect in preschool children with asthma [52].

Periodic treatment with ICS or montelukast

The two main drug alternatives for periodic treatment, *i.e.* ICS and montelukast, have been compared in a US multicentre study [53]. The study was carried out within the Childhood Asthma Research and Education (CARE) network, which is supported by the National Heart, Lung, and Blood Institute and is independent of the pharmaceutical industry. Periodic treatment with nebulised budesonide and montelukast was studied in preschool wheezers. The subjects were aged 1–5 years and had intermittent wheezing in connection with viral infections. The parents started the treatment at the first signs of a cold. All children, including the placebo group, received salbutamol as a bronchodilator.

The periodic treatment did not increase the percentage of symptom-free days, but both treatment alternatives reduced symptom severity [53]. For example, the total symptom score was reduced by 25–30%. There were no significant differences between the budesonide and montelukast groups.

Budesonide, as well as montelukast, was most likely to have a positive effect if the child had a positive API. In children with a negative API, that is viral wheeze, the effect was not statistically significant.

In a Canadian study, preschool children with virus-induced asthma received periodic treatment with high-dose nebulised fluticasone [38]. Compared with placebo, periodic treatment with nebulised fluticasone reduced the number of oral corticosteroid treatments. However, enthusiasm for these positive results has been tempered by findings of weight gain and reduction in linear growth among children in the fluticasone group [54].

The European Respiratory Society (ERS) Task Force on preschool wheeze suggested that periodic treatment with a leukotriene antagonist could be tried in the treatment of episodic viral wheeze [5]. However, a recent Global Initiative for Asthma (GINA) report questions the use of periodic

treatment with ICS, leukotriene antagonists and oral steroids in intermittent episodic wheezing, in children in whom a diagnosis of asthma cannot be confirmed [20]. If the child is considered to have "true" asthma, the GINA report recommends maintenance treatment with a low dose of ICS. A positive treatment effect can then be regarded as verifying the asthma diagnosis.

Taken together, the available data indicate that, as a general rule, the treatment effect in episodic viral wheeze is, at best, modest. The effect that is obtained has to be evaluated in relation to the drug costs and possible side-effects.

Reason for differences in treatment effects

The reason why the effect of ICS is usually poorer in episodic viral wheeze than in asthma with eczema or allergic sensitisation is probably due to different airway inflammation. In viral wheeze without eczema or allergic sensitisation, neutrophil leukocytes are usually found in bronchoalveolar lavage [55, 56]. In contrast, in asthma with allergic sensitisation, eosinophils are found in bronchoalveolar lavage, even if the symptoms are triggered by a viral infection [55, 56]. Corticosteroids effectively downregulate eosinophil inflammation but have little or no effect on neutrophils and neutrophil-associated cytokines such as interleukin-8 [57].

Treatment of exacerbations

At the start of an airway infection, or in conjunction with an occasional deterioration in children receiving maintenance treatment with ICS, the dose should be tripled or quadrupled for 7–10 days. The ICS dose–response curve is steep in the low dose range, and thereafter, fairly flat; thus, a substantial dose increase is needed to obtain an additive effect. If possible, the increased dose should be divided into three to four doses a day. In the event of an acute deterioration, a short-acting β_2-agonist can be given every 3–4 hours. If the effect is unsatisfactory, the parent should take the child to a physician or the emergency room.

Oral steroids in acute virus-induced wheezing

In a placebo-controlled trial, PANICKAR *et al.* [58] found no benefit of oral prednisolone in children aged 10 months to 5 years who were hospitalised with acute wheezing associated with a viral infection. Likewise, JARTTI *et al.* [59] found that prednisolone did not reduce the duration of hospitalisation in children aged 3 months to 3 years in whom the first or second episode of wheezing had been induced by rhinovirus or RSV. However, prednisolone decreased relapses during the subsequent 2-month period in the rhinovirus-affected children and in children with blood eosinophils $\geqslant 0.2$ cells $\times 10^9 \cdot L^{-1}$. As could be expected, rhinovirus-affected children had higher blood eosinophil levels, a higher prevalence of atopy and were older than the RSV-affected children [59]. In rhinovirus-affected children experiencing their first episode of wheezing, but not in RSV-affected children, prednisolone reduced recurrent wheezing (*i.e.* at least three episodes) during the subsequent year [60]. Prednisolone also reduced the likelihood of recurrent wheezing in children with eczema [60].

Drug delivery

Inhalation therapy is the preferred delivery route for β_2-agonists and corticosteroids. In the case of β_2-agonists, inhalation produces rapid symptom relief and, in the case of both β_2-agonists and corticosteroids, the inhaled route minimises systemic side-effects. For both infants and preschool children, pressurised metered-dose inhalers (pMDIs) are used with valved spacers (with or without a face mask, depending on the age of the child). Several spacer alternatives are available. Generally, nebulisers offer no advantages over pMDIs with spacers. In contrast, a pMDI with a spacer is easier to handle and costs less. However, treatment with nebulisers can be considered in some infants and young children with severe asthma and in children who, for various reasons, are unable to manage to use a spacer.

Treatment of gastro-oesophageal reflux

Gastro-oesophageal reflux is fairly common in young children with wheezing and it has been reported that controlling gastro-oesophageal reflux improves morbidity and reduces the need for daily asthma medication [61]. However, it has been claimed that a cause and effect relationship has not been proven [62]. The ERS Task Force concluded that a beneficial effect of treating gastro-oesophageal reflux in infants with wheeze has not been demonstrated [5].

Treatment algorithms

Organisations such as GINA and the national societies for paediatric allergology and respiratory medicine provide guidelines for the treatment of asthma in various age groups. The graphical algorithms in these guidelines are useful to the paediatrician in daily clinical work. An example of such an algorithm is presented in figure 1. It originates from the guidelines of the Swedish Society for Paediatric Allergology for the maintenance treatment of asthma in children [63]. The figure is based on the treatment algorithm for wheezing disorder/asthma in the 0–5-year age group.

Comments on the treatment algorithm

Step 1

Infants and preschool children who only have mild or moderate wheeze in conjunction with a cold are recommended to use a short-acting β_2-agonist for symptom relief. The β_2-agonist should preferably be delivered *via* a spacer.

Step 2

In children with more severe or recurrent respiratory infection-induced wheeze, periodic treatment with ICS or montelukast can be tried. Unfortunately, there is no way to find out which drug works best other than by trialling them. Treatment with ICS or montelukast should be started when the first signs of a cold appear. For example, if ICS is used, the Swedish guidelines recommend 125 μg of fluticasone four times a day for 3–4 days, followed by 125 μg twice a day for another 7 days. The dose for montelukast is 4 mg once a day for approximately 10 days.

If an evaluation of treatment response suggests that a treatment is not working, it should be discontinued and the other drug can be tried.

Step 3

Maintenance treatment is recommended for children who also experience symptoms between viral respiratory infections. Signs of atopy or a positive API strengthen the indication for maintenance treatment. These children are more likely to respond to treatment and the wheezing is more likely to represent ''true'' asthma. ICS or montelukast can be used; 4 mg of montelukast once a day is the alternative to low-dose ICS.

Treatment with ICS can be started with 50–125 μg of fluticasone twice a day. The dose should be continued for at least 1 month after the child has become symptom-free. Thereafter, the lowest effective dose can be titrated. The treatment response in a child who has started medication with ICS or montelukast should be evaluated after 6–8 weeks.

As colds are the most important triggers of asthma deteriorations in infants and preschool children, the summer is a good period in which to try a reduction of, or even an intermission in, medication in a symptom-free child. If, or when, asthma symptoms return, medication should be re-instituted or the higher dose should be resumed.

The height of all children receiving maintenance treatment with ICS should be measured once or twice a year. ICS at low or moderate doses rarely affect linear growth, but a height curve that is levelling off requires further investigation.

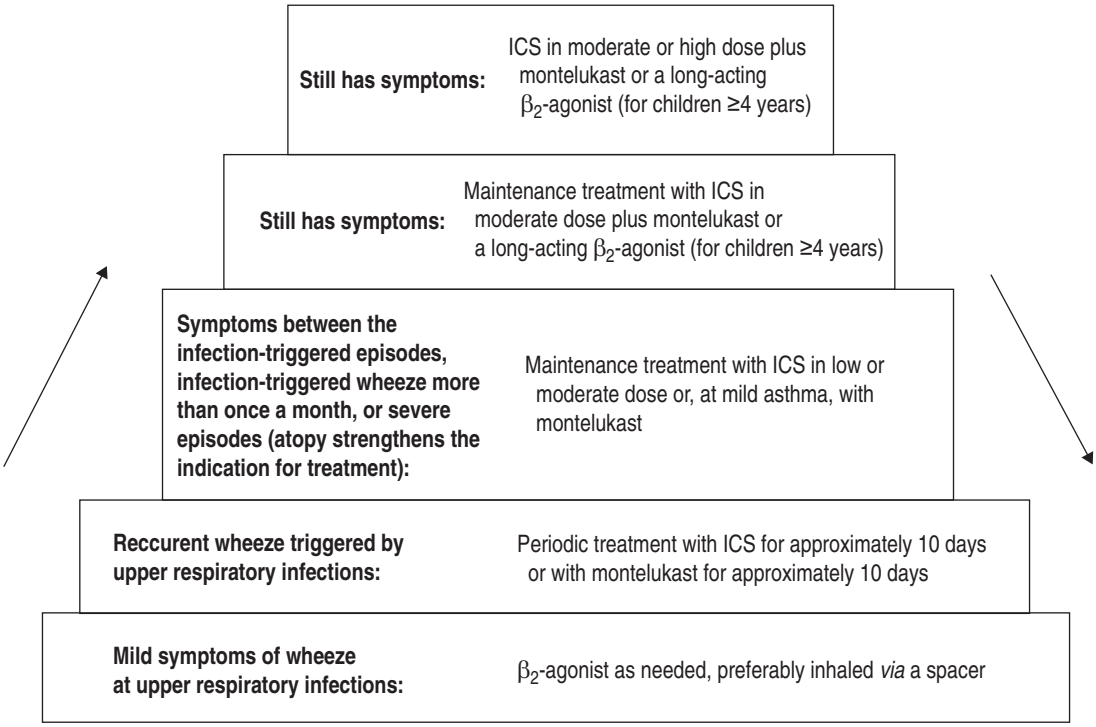
Still has symptoms:
ICS in moderate or high dose plus montelukast or a long-acting β_2-agonist (for children ≥4 years)
Still has symptoms:
Maintenance treatment with ICS in moderate dose plus montelukast or a long-acting β_2-agonist (for children ≥4 years)
Symptoms between the infection-triggered episodes, infection-triggered wheeze more than once a month, or severe episodes (atopy strengthens the indication for treatment):
Maintenance treatment with ICS in low or moderate dose or, at mild asthma, with montelukast
Reccurent wheeze triggered by upper respiratory infections:
Periodic treatment with ICS for approximately 10 days or with montelukast for approximately 10 days
Mild symptoms of wheeze at upper respiratory infections:
β_2-agonist as needed, preferably inhaled *via* a spacer

Figure 1. Algorithm for the treatment of asthma/wheeze in infants and preschool children (aged 0–5 years). At all levels, a β_2-agonist is given for symptom relief. The algorithm is based on the 2009 guidelines of the Swedish Society for Paediatric Allergology [63]. ICS: inhaled corticosteroids.

Step 4

If the child still has asthma symptoms, the recommendation is to combine ICS (*e.g.* 200–250 μg of fluticasone twice a day) and montelukast. Alternatively, ICS can be combined with a long-acting β_2-agonist provided that the child has reached an age at which long-acting β_2-agonists are available (currently 4 years of age in Sweden for salmeterol).

Step 5

If there are still symptoms at step 4, the ICS dose should be further increased (*e.g.* to 250–400 μg of fluticasone a day).

For some infants and young children with uncontrolled asthma, ICS *via* a nebuliser can be tried. The starting dose is 250–500 μg of budesonide twice a day.

In children with an insufficient response to treatment, adherence should be evaluated. A liberal attitude towards re-assessment of the asthma diagnosis is recommended, and radiographs and an extended laboratory work-up may be required. A foreign body, vascular ring, lung malformation, tumour causing bronchial obstruction, or a disease such as cystic fibrosis may produce respiratory symptoms that can be mistaken for asthma. Severe asthma is discussed further in the chapter by HEDLIN *et al.* [64].

GINA guidelines

The GINA report recommends a low-dose ICS as the preferred initial treatment to control asthma in children aged ⩽5 years (table 1) [20].

The GINA report suggests that the initial treatment should be given for at least 3 months to establish its effectiveness in achieving control. If, at the end of the period, the low dose of ICS does not control symptoms, and the child is using the optimal technique and is adherent to therapy, the

GINA report recommends that doubling the initial ICS dose may be the best option. The addition of montelukast to the low-dose ICS may also be considered, although the authors point out that this has not been studied in this young age group. Furthermore, the best treatment for children whose asthma is not controlled on twice the initial dose of ICS has not yet been established. Options to consider, according to GINA, are to further increase the dose of ICS or to add montelukast [20].

Table 1. Low daily doses of inhaled corticosteroids for children aged ⩽5 years

Drug	Low daily dose[#] μg
Beclomethasone dipropionate	100
Budesonide MDI + spacer	200
Budesonide nebulised	500
Ciclesonide	NS
Fluticasone propionate	100
Mometasone furoate	NS
Triamcilone acetonide	NS

MDI: metered-dose inhaler; NS: not studied in this age group. [#]: defined as the dose that has not been associated with clinically adverse effects in trials including measures of safety. This is not a table of clinical equivalence. Reproduced from [20] with permission from the publisher.

If, in children with seasonal symptoms, daily long-term control therapy is discontinued after the season, a written action plan is recommended. The plan should describe signs of worsening asthma and the therapeutic interventions that should be initiated. Furthermore, GINA recommends that the continued need for asthma treatment should be regularly assessed in children aged <5 years of age every 3–6 months. A follow-up visit is recommended 3–6 weeks after the discontinuation of therapy to ascertain whether the remission of symptoms persists and whether there is no need for the re-institution of therapy.

Conclusions

Many infants and preschool children have asthmatic symptoms with wheezing. Asthma episodes are predominantly triggered by colds. However, the pathogenesis of wheezing disorder in this young age group is heterogeneous.

A large group of young children only wheeze in conjunction with colds. Other children also wheeze between colds. These children often have an atopic component and are the children that tend to develop ''true'' asthma.

The heterogeneity of asthma in infants and preschool children is reflected by the fairly varied effectiveness of asthma medication. As a group, children with signs of atopy and children who also wheeze between colds respond positively to ICS, while the effect of ICS is often unsatisfactory in viral wheeze. Periodic treatment with ICS or with montelukast has been shown to reduce symptoms to some degree in preschool wheezers with intermittent wheezing in connection with viral infections. However, the available data indicate that, as a general rule, the treatment effect in episodic viral wheeze is, at best, modest.

Statement of Interest

G. Wennergren has received fees for lectures from Novartis, Merck Sharp & Dohme, AstraZeneca and GlaxoSmithKline. He does not hold any stocks or shares in any pharmaceutical company.

References

1. Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332: 133–138.
2. Alm B, Erdes L, Möllborg P, *et al.* Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics* 2008; 121: 697–702.
3. Castro-Rodriguez JA, Rodriguez-Martinez CE, Custovic A. Infantile and preschool asthma. *Eur Respir Monogr* 2012; 56: 10–21.

4. Lødrup Carlsen KC, Carlsen KH. Asthma in children: the road to individual asthma phenotypes. *Eur Respir Monogr* 2012; 56: 1–9.
5. Brand PL, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096–1110.
6. Sonnappa S, Bastardo CM, Wade A, *et al.* Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010; 126: 519–526.
7. Schultz A, Devadason SG, Savenije OE, *et al.* The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010; 99: 56–60.
8. Strachan DP, Cook DG. Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997; 52: 905–914.
9. Lannerö E, Wickman M, Pershagen G, *et al.* Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res* 2006; 7: 3.
10. Goksör E, Åmark M, Alm B, *et al.* Asthma symptoms in early childhood – what happens then? *Acta Paediatr* 2006; 95: 471–478.
11. Goksör E, Åmark M, Alm B, *et al.* The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. *Acta Paediatr* 2007; 96: 1030–1035.
12. Kull I, Wickman M, Lilja G, *et al.* Breast feeding and allergic diseases in infants – a prospective birth cohort study. *Arch Dis Child* 2002; 87: 478–481.
13. Elliott L, Henderson J, Northstone K, *et al.* Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). *J Allergy Clin Immunol* 2008; 122: 49–54.
14. Kull I, Almqvist C, Lilja G, *et al.* Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004; 114: 755–760.
15. Goksör E, Alm B, Thengilsdottir H, *et al.* Preschool wheeze – impact of early fish introduction and neonatal antibiotics. *Acta Paediatr* 2011; 100: 1561–1566.
16. Hesselmar B, Åberg N, Åberg B, *et al.* Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999; 29: 611–617.
17. Wegienka G, Johnson CC, Havstad S, *et al.* Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. *Clin Exp Allergy* 2011; 41: 979–986.
18. Almqvist C, Egmar AC, van Hage-Hamsten M, *et al.* Heredity, pet ownership, and confounding control in a population-based birth cohort. *J Allergy Clin Immunol* 2003; 111: 800–806.
19. Hederos CA, Janson S, Hedlin G. Group discussions with parents have long-term positive effects on the management of asthma with good cost-benefit. *Acta Paediatr* 2005; 94: 602–608.
20. Global Initiative For Asthma. Global strategy for diagnosis and management of asthma in children 5 years and younger. www.ginasthma.org/Guidelines/guidelines-global-strategy-for-the-diagnosis.html Date last updated: May 1, 2009. Date last accessed: July 12, 2011.
21. Prendiville A, Green S, Silverman M. Airway responsiveness in wheezy infants: evidence for functional β-adrenergic receptors. *Thorax* 1987; 42: 100–104.
22. Kraemer R, Frey U, Sommer CW, *et al.* Short-term effect of albuterol, delivered *via* a new auxiliary device, in wheezy infants. *Am Rev Respir Dis* 1991; 144: 347–351.
23. Holmgren D, Bjure J, Engström I, *et al.* Transcutaneous blood gas monitoring during salbutamol inhalations in young children with acute asthmatic symptoms. *Pediatr Pulmonol* 1992; 14: 75–79.
24. Hofhuis W, van der Wiel EC, Tiddens H, *et al.* Bronchodilation in infants with malacia or recurrent wheeze. *Arch Dis Child* 2003; 88: 246–249.
25. Prendiville A, Rose A, Maxwell DL, *et al.* Hypoxaemia in wheezy infants after bronchodilator treatment. *Arch Dis Child* 1987; 62: 997–1000.
26. Primhak RA, Smith CM, Yong SC, *et al.* The bronchoprotective effect of inhaled salmeterol in preschool children: a dose-ranging study. *Eur Respir J* 1999; 13: 78–81.
27. Nielsen KG, Bisgaard H. Bronchodilation and bronchoprotection in asthmatic preschool children from formoterol administered by mechanically actuated dry-powder inhaler and spacer. *Am J Respir Crit Care Med* 2001; 164: 256–259.
28. Russell G, Williams DA, Weller P, *et al.* Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995; 75: 423–428.
29. Byrnes C, Shrewsbury S, Barnes PJ, *et al.* Salmeterol in paediatric asthma. *Thorax* 2000; 55: 780–784.
30. Sekhsaria S, Alam M, Sait T, *et al.* Efficacy and safety of inhaled corticosteroids in combination with a long-acting β2-agonist in asthmatic children under age 5. *J Asthma* 2004; 41: 575–582.
31. Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007; 42: 407–420.
32. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123: e519–e525.
33. Teper AM, Kofman CD, Szulman GA, *et al.* Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. *Am J Respir Crit Care Med* 2005; 171: 587–590.

34. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354: 1985–1997.
35. Castro-Rodriguez JA, Holberg CJ, Wright AL, *et al.* A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162: 1403–1406.
36. Guilbert TW, Morgan WJ, Krawiec M, *et al.* The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials* 2004; 25: 286–310.
37. Svedmyr J, Nyberg E, Thunqvist P, *et al.* Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999; 88: 42–47.
38. Ducharme FM, Lemire C, Noya FJ, *et al.* Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009; 360: 339–353.
39. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995; 72: 317–320.
40. Ilangovan P, Pedersen S, Godfrey S, *et al.* Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. *Arch Dis Child* 1993; 68: 356–359.
41. Bisgaard H, Allen D, Milanowski J, *et al.* Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004; 113: e87–e94.
42. Bisgaard H, Hermansen MN, Loland L, *et al.* Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; 354: 1998–2005.
43. Murray CS, Woodcock A, Langley SJ, *et al.* Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006; 368: 754–762.
44. Devulapalli CS, Carlsen KC, Håland G, *et al.* Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008; 63: 8–13.
45. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. *Am J Respir Crit Care Med* 2000; 162: 187–190.
46. Hakim F, Vilozni D, Adler A, *et al.* The effect of montelukast on bronchial hyperreactivity in preschool children. *Chest* 2007; 131: 180–186.
47. Knorr B, Franchi LM, Bisgaard H, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001; 108: e48.
48. Bisgaard H, Zielen S, Garcia-Garcia ML, *et al.* Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315–322.
49. Robertson CF, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 175: 323–329.
50. Szefler SJ, Baker JW, Uryniak T, *et al.* Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol* 2007; 120: 1043–1050.
51. Bisgaard H, Flores-Nunez A, Goh A, *et al.* Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008; 178: 854–860.
52. van der Wouden JC, Tasche MJ, Bernsen RM, *et al.* Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev* 2003; 3: CD002173.
53. Bacharier LB, Phillips BR, Zeiger RS, *et al.* Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127–1135.
54. Chipps BE, Bacharier LB, Harder JM. Phenotypic expressions of childhood wheezing and asthma: implications for therapy. *J Pediatr* 2011; 158: 878–884.e1.
55. Stevenson EC, Turner G, Heaney LG, *et al.* Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; 27: 1027–1035.
56. Marguet C, Jouen-Boedes F, Dean TP, *et al.* Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. *Am J Respir Crit Care Med* 1999; 159: 1533–1540.
57. Benson M, Strannegård I-L, Strannegård Ö, *et al.* Topical steroid treatment of allergic rhinitis decreases nasal fluid TH2 cytokines, eosinophils, eosinophil cationic protein, and IgE but has no significant effect on IFN-γ, IL-1β, TNF-α, or neutrophils. *J Allergy Clin Immunol* 2000; 106: 307–312.
58. Panickar J, Lakhanpaul M, Lambert PC, *et al.* Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009; 360: 329–338.
59. Jartti T, Lehtinen P, Vanto T, *et al.* Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006; 25: 482–488.
60. Lehtinen P, Ruohola A, Vanto T, *et al.* Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J Allergy Clin Immunol* 2007; 119: 570–575.
61. Sheikh S, Stephen T, Howell L, *et al.* Gastroesophageal reflux in infants with wheezing. *Pediatr Pulmonol* 1999; 28: 181–186.

62. Mathew JL, Singh M, Mittal SK. Gastro-oesophageal reflux and bronchial asthma: current status and future directions. *Postgrad Med J* 2004; 80: 701–705.
63. Swedish Society for Paediatric Allergology. Underhållsbehandling av astma hos barn [Guidelines for maintenance treatment of asthma in children]. www.barnallergisektionen.se/stenciler_nya06/underhallsbeh_astma_090822.pdf Date last updated: August 22, 2009. Date last accessed: July 26, 2011.
64. Hedlin G, de Benedictis FM, Bush A. Problematic severe asthma. *Eur Respir Monogr* 2012; 56: 22–39.

Chapter 17

Treatment of asthma from childhood to adulthood

Jorrit Gerritsen and Bart Rottier

SUMMARY: Treatment of chronic asthma throughout childhood ranges from primary preventive therapy from birth to drug treatment, either intermittently or on a daily basis. Treatment of childhood asthma is focused on reducing symptoms and the assessment of as normal as possible daily life. Inhaled corticosteroids (ICS) are effective in modifying the disease but do not cure asthma. The knowledge about the deposition of inhalant medication, especially in young children, is very limited and many problems have to be elucidated in future research.

KEYWORDS: Allergy, childhood asthma, lung deposition, treatment

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In the first consensus statement on the management of asthma, asthma was defined as ''episodic wheeze and/or cough in a clinical setting where asthma is likely and other rarer conditions have been excluded'' [1]. For this initial consensus statement, a round-table conference with 26 specialists from around the world was organised in London, UK. In the final document no references were published and all recommendations were based on expert opinion. Since then many international and national statements and guidelines have been published, of which some are evidence based, some are consensus based and some are implemented in the daily management of children and adults with asthma [2–5]. The initial definition of asthma was highly descriptive, whereas nowadays, the definition of asthma includes pathophysiology, as it is a multifactorial chronic inflammatory disease of the airways. Alternatively, MURPHY and O'BYRNE [6] defined asthma as a chronic inflammatory disorder of the airways characterised by reversible airway obstruction, airway hyperresponsiveness (AHR), infiltration of eosinophils and T-helper type 2 (Th2) cells into the airway sub mucosa, mucus hypersecretion and airway remodelling [7].

In the first consensus statement, a step-wise approach was suggested for three age groups, 1–3, 3–5 and 5–15 years, and lung function had a prominent role in deciding the severity of asthma and, subsequently, on treatment. In the latest edition of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines [2], age classification is still being used and asthma is considered as a clinical diagnosis in which signs and symptoms can increase or decrease the probability of asthma [3].

Primary and secondary prophylactic treatment

Environmental exposure

In the first consensus statement, prevention was one of the main steps in the treatment of allergy and asthma. Primary and secondary interventional strategies are predominantly based on observational studies. Most studies are multifaceted and from these studies, it is hardly possible to disentangle the effects of the different forms of exposures and their impact on the development or progression of allergy.

Exposure to high levels of house dust mite allergen in early life in susceptible children is associated with an increased likelihood of sensitisation to house dust mite by 3–7 years of age [8]. In several studies, sensitisation to house dust mite has been assessed as an important factor for the development of asthma and allergy [9, 10]. The studies investigating intervention, even when placebo controlled, do not support the belief that early environmental control influences the development of allergy and asthma both in susceptible and non-susceptible children [11–17]. Close contact with a cat or a dog early in life has been found to be a factor that reduces the subsequent development of allergy and asthma [18, 19].

It can be concluded that there is no consistent evidence of the benefit of domestic aeroallergen avoidance on the development of allergy and asthma. Therefore, in general, this cannot be recommended for preventing childhood asthma.

Feeding

Although sensitisation to foods, especially eggs, precedes the development of allergy to aeroallergens and asthma, there is no evidence that food allergen avoidance during pregnancy prevents the development of allergy and asthma [20–23].

Breastfeeding is effective for all children and not related to allergy heredity. The effect is more pronounced in high-risk infants when they are breastfed for at least 4 months [24, 25]; however, the findings are not consistent, as demonstrated in a large cohort. Nevertheless, breastfeeding should be encouraged due to the many benefits, and it may also have a potential protective effect in relation to early asthma.

Studies on the effects of modified infant milk formulae as a tool to prevent the development of allergy and asthma are inconclusive. In the absence of any evidence of benefit it should not be recommended. Aspects on primary intervention are covered in more detail in the chapters by LAU *et al.* [26, 27].

Diagnosis and treatment of asthma in preschool children

Diagnosis of asthma at an early age is still difficult to ascertain and is currently under debate. In fact, most studies in this age group focus on wheezing and describe asthma as a wheezing disorder. Preschool wheeze can be divided in two different phenotypes: episodic viral wheeze (EVW) and multiple-trigger wheeze [28]. The complete spectrum of wheezing, *i.e.* episodic, viral and atopic, *etc.*, has been discussed extensively in the chapter by CASTRO-RODRIGUES *et al.* [29]. Following the European Respiratory Society Task Force on wheeze, it has become clear that, in general, preschool children will track their phenotype, but also may switch from one phenotype of wheeze to the another [28, 30]. In addition, a systematic review of inhaled corticosteroid (ICS) studies in preschool wheezing showed that ICS were effective in these patients, irrespective of their clinical phenotype [31]. Finally, it has been shown that 90% of all wheezing episodes are provoked by viral infections [32]. Although ICS are effective for symptom control, early intervention studies with ICS, either intermittently during wheezing episodes or regularly, showed no effect in preventing progression and/or development of any form of preschool wheeze to asthma in childhood [33–35]. Daily low-dose budesonide in preschool children with recurrent wheezing is not superior to an

intermittent high-dose regimen in reducing asthma exacerbations but did result in a higher cumulative dose of ICS at 1 year of age. The jury is still out regarding the harm–benefit balance of this approach. This study confirms the uncertainties on the effects of corticosteroid treatment in this age group but also focuses on the risks, especially in infants receiving high doses [36].

Treatment of asthma in schoolchildren and beyond

The spectrum of asthma symptoms changes with increasing age and the diagnosis can be more easily assessed at a later age. The diagnosis of asthma is clinical; therefore, there is no standardised definition of the type, severity or frequency of symptoms, or of the investigative findings of eosinophils, total and specific immunoglobulin (Ig)E, and lung function, *etc.* However, the absence of a gold standard definition does not mean that it is not possible to make clear evidence-based recommendations on how to diagnose asthma. The BTS guidelines have extensively presented ways in which a diagnosis of asthma can be made [2]. The role of lung function and allergy testing in the diagnosis of asthma is very limited. Lung function has an important role in indicating the degree of bronchial obstruction and the severity of asthma. Thereby asthma is, as already stated, a clinical diagnosis and the diagnosis relies on the respiratory symptoms. For the diagnosis and follow-up of asthma, information about the reversibility of bronchial obstruction by objectifying bronchodilator response to β_2-agonists has to be assessed [4]. The role of measuring exercise-induced bronchial obstruction and bronchial hyperreactivity in the diagnosis of and follow-up treatment response in asthma is presented in the chapters by CARLSEN and LØDRUP-CARLSEN[37] and ROUKEMA *et al.* [38].

As soon as a diagnosis of asthma is confirmed, the aim of treatment is to achieve good asthma, meaning that: 1) patients have few or preferably no asthma-related symptoms during the day and none at night; 2) reliever medication is only needed occasionally, for example, less than three times a week; 3) patients have no activity limitation at school or during sport; 4) the forced expiratory volume in 1 second (FEV_1) is normal, *i.e.* the patient's personal best, and bronchial obstruction is measured by the FEV_1 as a percentage of vital capacity (VC); and 5) patients have no or only a minimum number of asthma exacerbations [3, 4].

Long-term improvement of asthma, lung function and AHR are not included in these treatment aims. In the short term, inhalation of corticosteroids has been proven to be effective in decreasing bronchial obstruction within a number of weeks with an improvement of FEV_1 of approximately 10%, and diminishing AHR with approximately two dosage steps both in children with asthma and adults with chronic obstructive pulmonary disease (COPD) [39–41]. However, cessation of inhaled corticosteroids (ICS) after 2 years of treatment resulted in deterioration of lung function within weeks and decreased AHR to the pre-study values. Thus, ICS only modify the disease but do not cure asthma [42–44]. These studies only investigated the overall effect of treatment and not the individual response.

In future, it will be necessary to focus on responders and non-responders to therapy and the differences in the phenotypes and genotypes, for example, of the corticosteroid and β_2-receptors of the airways.

In the first consensus statement on the treatment of childhood asthma, a stepwise approach was suggested based on age categories and severity of the disease. This approach was repeated in the subsequent publications on this topic and also in the recently published BTS guidelines [1, 2]. These guidelines are important in obtaining an understanding of the general approach of these patients; however, in daily practice, the assessment of disease severity and the choice of treatment relies heavily on personal experience, and interpretation of the disease can be seen as a continuum from mild intermittent to mild-to-moderate, to moderate severe and to severe asthma. All schedules start in mild intermittent asthma with short-acting β_2-agonists as required. The subsequent step is starting regular ''preventer'' therapy. There is still debate as to whether the first choice should be a leukotriene antagonist or an ICS, especially in the younger age group. In children aged $\leqslant 4$ years, initiating treatment with a leukotriene antagonist has been proven to

be effective [45]. In children, especially in preschool children, regression of asthma can occur spontaneously; therefore, an intermittent trial of ICS reduction is warranted [46]. In mild persistent asthma when asthma control is achieved, the use of rescue ICS with β_2-agonists can be an effective and also a safe method of tapering off therapy [47]. The advantage is that it reduces the ICS-related growth suppression [46, 48]. However, it is more related to therapy compliance and adherence, as discussed in chapter by KLOK *et al.* [49].

ICS play a central role in the control of asthma at all ages, from infancy through to adulthood [50–52]. ICS are more effective than leukotriene receptor antagonists [53].

In 1933, FINEMAN [54] was the first to administer extracts of adrenal glands in the treatment of asthma. Several studies focused on the role of adrenocorticotropic hormone (ACTH) and systemic corticosteroids in the treatment of asthma. In 1972, BROWN *et al.* [55] reported, for the first time, on the effectiveness of inhaled beclomethasone diproprionate for the treatment of allergic asthma. This study included four children aged, 9, 11, 13 and 15 years with severe asthma who were receiving daily oral corticosteroids. In these children, oral corticosteroids could be discontinued and replaced by treatment with beclomethasone diproprionate. An improvement in peak flow values was measured in all four children. This success has been followed by more than 1,100 clinical trials in children with first and subsequent generations of ICS. The studies on the molecular and anti-inflammatory signalling mechanisms and the cellular effects are mainly from adult and animal studies and are discussed in a recent clinical review by DE BENEDICTIS and BUSH [51]. 40 years after the introduction of ICS in children only limited information is available about the pharmacokinetics of ICS, the phenotypes and genotypes of responders and non-responders, and the deposition of the drug in the airways, especially in children aged <6 years. In general, it is important to realise that in studies, the effects of drugs are generally described on a group level, whereas the response generally looks like a bell-shaped curve demonstrating that, although most subjects improve with drug treatment, some benefit to a larger extent than average, whereas in others an opposite effect can be observed (fig. 1) [56].

Lung deposition of inhaled drugs generally increases with age, which is the reason why, in general, children and adults can use the same nominal dose, as has been described for budesonide [57, 58]; however, for young infants with the nose as an effective filter the dose needed might be higher.

Therefore, from the onset the same ICS dosages are used in children as in adults because no real dose-finding studies are available. ICS are very effective, and maintenance treatment with ICS controls asthma symptoms, reduces the frequency of acute exacerbations and the number of hospital admissions, improves quality of life and lung function, and decreases AHR and indirect markers of inflammation [59, 60]. The bioavailability of the ICS differs as lipophilicity, lung delivery profiles and pharmacodynamics vary widely between the available ICS [61]. Improvement of symptoms and control of asthma is, in the majority of children, observed at moderate

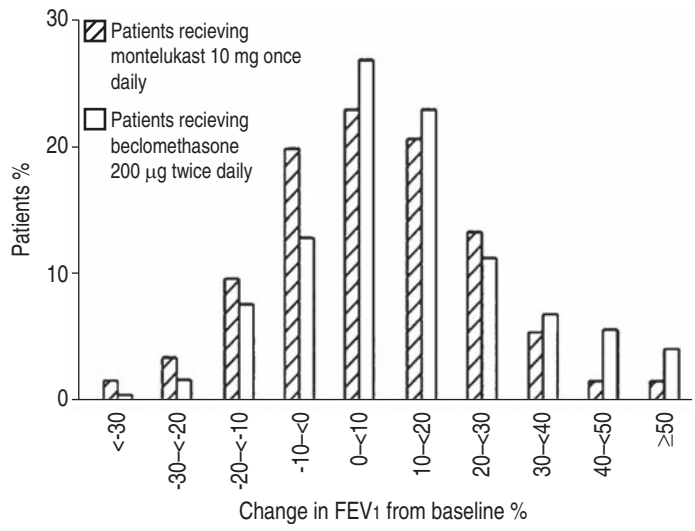

Figure 1. Distribution of treatment responses for forced expiratory volume in 1 second (FEV1). The response distributions are shown for predefined intervals of percentage change in FEV1. Reproduced from [56] with permission from the publisher.

doses of different ICS. In most instances, high dosages of ICS are not needed and are not more effective in comparison with lower doses [62].

The dose–response curve for ICS treatment begins to flatten for many efficacy measures at low-to-medium doses, although some data suggest that higher doses may reduce the risk of exacerbations. Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dosage (fig. 2).

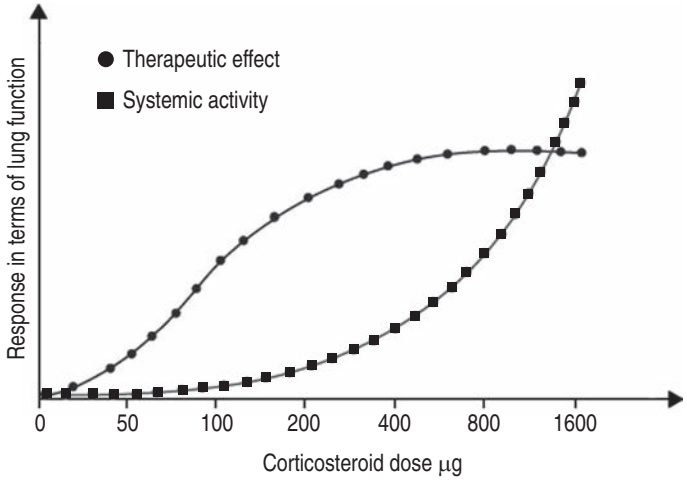

Figure 2. Dose–response curve effect of inhaled corticosteroids (beclomethasone or equivalent) in asthma. Reproduced from [63] with permission from the publisher.

How to proceed with asthma not controlled with ICS

First, the diagnosis and comorbid conditions should be reviewed. Secondly, the level of adherence should be considered. Only after review of inhalation technique and consideration of changing the drug or device can a choice be made on step-up therapy.

The diagnosis of asthma should at least be given some consideration on the basis of history and physical examination. In addition, comorbid conditions such as allergic rhinitis, breathing abnormalities and tracheomalacia should be considered [64, 65]. An alternative diagnosis or a comorbid condition should be treated accordingly (*e.g.* nasal steroid for allergic rhinitis). Following this, persistent exposure to irritants (especially cigarette smoke [66]) or allergens to which the child is sensitised should be taken into account. Exercise-induced dyspnoea is often reported, but is usually not caused by asthma treated with ICS. If exercise-induced dyspnoea is not responsive to pre-treatment with β_2-agonists then it is probably not due to exercise-induced bronchoconstriction (EIB), in which case normal physiological exercise limitation or poor conditioning should be considered [67]. Careful evaluation of exercise-induced dyspnoea is required by objective measurement, *i.e.* standardised exercise tests [37]. Furthermore, restrictive abnormalities, tracheomalacia or exercise-induced laryngeal obstruction can cause dyspnoea on exertion. Over-reporting of symptoms may lead to overtreatment.

Long-acting β_2-agonists

In one of the first studies in children comparing salmeterol and ICS over the course of 1 year, it was evident that ICS (beclomethasone) was superior to salmeterol in children with mild-to-moderate chronic asthma [68]. In the early 1990s there was concern about the use of long-acting β_2-agonists (LABAs) as monotherapy for asthma as a deleterious effect was observed in some patients [69]. This has resulted in the advice of using add-on therapy with LABA as first-line treatment for persistent asthma. A clinical trial was designed that examined whether combinations of ICS and LABA changed the risks of severe asthma exacerbations; using the combination of budesonide and formoterol significantly reduced the risks of both mild and severe asthma exacerbations when compared with the same doses of ICS alone [70]. This has been reproduced in many studies using this and other combinations of ICS and LABAs [71–73]. It also has been studied in children aged 12 years and over with a mixture of ICS and LABA. In the FACET (Formoterol and Cortocosteroids Establishing Therapy) trial, the addition of formeterol to ICS therapy significantly reduced the annual rate of exacerbation and mean symptom score at night

and during the day. It increased FEV1 and the benefit of adding formoterol to budesonide was observed irrespective of the budesonide dose [70].

It can be concluded that the first choice in the treatment of chronic persistent asthma is ICS and, if this is not effective, LABA as add-on therapy. However, several times the second step of the BTS guidelines is bypassed in 25% of children due to the prescription of LABA/ICS fixed-dose combination without prior prescription of an ICS. This policy is not supported by the evidence and must be discouraged.

Whereas the BTS and Global Initiative for Asthma (GINA) guidelines both prefer to add LABA to ICS instead of increasing the ICS dose in the third step, in the Netherlands, we recently changed our consensus-based phenotypic approach, after a Cochrane analysis, to one favouring initial doubling of the ICS dose (from the generally recommended starting doses of ICS) [2–5, 73]. Although LABAs have the best chance of improving asthma control at a group level compared to adding anti-leukotrienes or doubling ICS, increasing ICS was chosen because of other key factors. A relatively high value was placed on the consideration that "new" medications should either be more effective or safer. Most studies show that the LABA–ICS option is not inferior to doubling the ICS dose. Adding LABA is more expensive than doubling ICS. Furthermore, it was generally considered easier to increase ICS and there were fewer safety concerns compared to LABA (both may be and were debated). Recent studies failed to predict a treatment response to LABA, a doubled dose of ICS or anti-leukotrienes by bronchodilatory response or level of exhaled nitric oxide fraction ($F_{E}NO$) [68, 74]. In conclusion, any approach may be tried as long as you evaluate the response to the chosen change of treatment and act accordingly. The safety of LABAs with ICS will be studied in a real life design in three randomised clinical trials in adolescents and adults and one trial in children aged 4–11 years comparing combination treatment *versus* ICS alone [75]. The trials will last 6 months and the results are expected in 2017.

The target of inhaled drug delivery in asthma

The site in the body where drugs are needed generally depends on the localisation of the disease process and the localisation of the receptors for the drug. β_2-agonists act on smooth muscle that is mainly located around the non-cartilaginous airways. Asthma is a disease where inflammation occurs in both the large and small airways, as explained previously. As the number of ICS receptors increases towards the lung periphery [76], targeting the small airways has been referred to as the new challenge of ICS treatment (fig. 3) [77]. In order to target the small airways, a large fine-particle fraction (particles with a diameter of 1–3 μm) is necessary as these particles provide a higher peripheral and total lung deposition than larger particles [78]. β_2-agonists have been proven to be more effective in the 3–6 μm range [78]. These deposition fractions were reached with a slow inhalation (mean 30.8 $L \cdot min^{-1}$), followed by a breath-hold period. Lung deposition is not only dependent on particle size, but also on inspiratory flow: particle deposition in the lungs shifts to the upper airways when the flow rate is increased. Only approximately 25% of the real dose of 1.5-μm

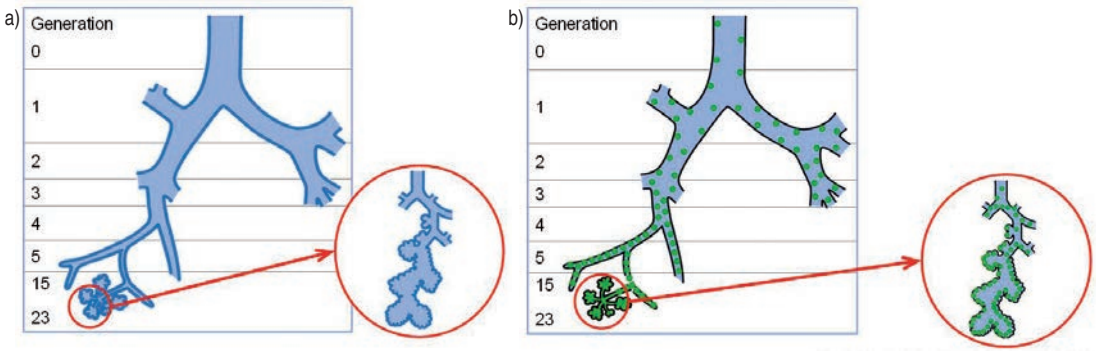

Figure 3. a) The inflammatory processes in asthma involve the entire bronchial tree up to the alveolar region. b) The number of corticosteroid receptors increases towards the periphery of the lung. Reproduced with permission from the ITW-Dutch Inhalation Technology working group.

particles deposit on 95% of the total lung surface area (in the peripheral lung) *versus* 31% of the real dose on the complementary 5% of the total surface area (in the central and intermediate lung) [79]. This yields a difference in concentration by a factor of almost 25. For larger particles or higher flow rates, the differences are even greater. These calculations are explained in more detail elsewhere [80], as the availability of ICS in pressurised metered-dose inhalers (pMDIs) differs greatly in relation to the produced particle size [81]. Although based on modelling studies and *in vitro* data, the use of ICS with a high small particle size fraction (1–3 μm) may be preferred over coarse-particle ICS; to date, patient studies have shown equivalence and no superiority of small-particle ICS.

Devices and deposition of drugs in asthma

The factors that mask a clear view of the dose–response relationship of ICS are asthma severity and duration of asthma (remodelling), baseline pulmonary function, and pharmacogenetic make-up. The influence of pharmacogenetic make-up has been demonstrated for both bronchodilatory response and, to a lesser extent, ICS [82–84]. This pharmacogenetic make-up is partly related to ethnicity. In preschool children outcomes are even more difficult to define, particularly as younger children cannot perform the more informative pulmonary function tests as the measurement of flow–volume loops cannot be performed.

Due to the factors that obscure a clear view of the dose–response relationship to ICS, information on deposition other than clinical effect is necessary. Information on the area of deposition for ICS can be obtained directly from studies of radiolabelled aerosols with gamma scintigraphy, using plasma sampling after an inhaled dose or urinary excretion. Information on deposition can also be obtained indirectly from artificial lung models of air trapping on expiratory computed tomography (CT) scans, the use of hyperpolarised helium with magnetic resonance imaging (MRI) to measure gas distribution, the measurement of lung clearance index, and endogenous cortisol suppression resistance as measured by pulmonary function tests [85–90]. The limitation of all these studies is that they are performed with different drug and devices and in different patient (age) groups. Therefore, the results cannot be generalised.

Four categories of devices for inhalation medication exist: pMDIs; breath-actuated inhalers; dry-powder inhalers (DPIs) and nebuliser systems [81, 91]. In childhood, valved holding chambers, also called ''spacers'', are used to overcome coordination problems. Valved holding chambers have either a face mask, which should have a closed fit, or a mouthpiece. As the nose is built as an efficient filter to protect the lungs, as soon as children can control breathing through their mouth a mouthpiece should be used. The lower aerosol plume velocity and higher temperature from hydrofluoroalkane (HFA) inhalers compared to chlorofluorocarbon (CFC) inhalers may influence aerosol behaviour in the spacer. As soon as the child is old enough, single-breath inhalation is advised instead of tidal breathing [92]. With the single-breath method, which is used with spacers and DPIs, the patient should first exhale to residual volume, followed by a single inhalation and a breath hold of 5–10 seconds to allow the drugs to settle in the airways [92]. Nebulisers should only be used when concomitant oxygen delivery is needed; otherwise pMDIs and spacers are just as effective if multiple doses of bronchodilators are given.

Compliance and adherence with asthma therapy

The first studies on compliance and adherence to asthma therapy in children and adults aimed to titrate the effect of medication on the dosages used [40, 41]. After patients returned the canisters they were weighed and the accounted dosages were compared with the prescribed. At that time a large discrepancy was found between patients in the study group, as the fully prescribed dosages varied from no dosages used in comparison to the prescribed ones. It became evident that the influence of the prescribing medical doctor is very limited and many ways to change this for the better have been undertaken. Adherence, as monitored by electronic monitoring devices in clinical trials in paediatric asthma, can be as low as 50% to 77% [93]. As participation in a trial usually increases adherence and symptom control, these percentages are presumably (much) lower in a non-selected asthmatic population. Participation in a trial usually increases adherence and symptom control, and most

non-adherent patients do normally not enrol in clinical trials [68]. The increase of adherence can, therefore, be considered as an effective and inexpensive way to improve disease and symptom control. Thereby, we have to realise that, especially in young children, most families are hectic during the starting phase and their first priority is finding time for the children, resulting in limited attention to compliance and adherence. This is discussed in more detail in the chapter by KLOK *et al.* [49], who also suggested methods that are available to break through this therapeutic dilemma.

Conclusions

International guidelines for the treatment of asthma are important and serve as tools and provide valuable hints for physicians, but should never be interpreted as dogmas. The role of different methods of primary intervention in the prevention and treatment of asthma is still to be elucidated. The knowledge about the deposition of inhaled medication in relation to clinical effects, especially in young children, is limited.

Despite effective therapy, many patients are not well-controlled because of the lack of adherence to medication. This can be considered as one of the challenges for improvement. Asthma symptoms can be treated effectively, but asthma cannot be cured.

Future directions

The drugs currently being developed for the treatment of asthma are discussed extensively in the chapter by SLY and JONES [94]. It is important that information about deposition of inhaled medication becomes available, especially in young children.

Statement of Interest
None declared.

References

1. Warner JO, Götz M, Landau LI, *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989; 64: 1065–1079.
2. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. A National Clinical Guideline. 2011. www.sign.ac.uk/pdf/sign101.pdf
3. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). 2011. Available from: www.ginasthma.org
4. Bacharier LB, Boner A, Carlsen KH, *et al.* Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63: 5–34.
5. Rottier BL, Brouwer ML, Janssens HM, *et al.* Drug maintenance treatment. *T Kindergeneesk.* 2009; 77: 243–249.
6. Murphy DM, O'Byrne PM. Recent advances in the pathophysiology of asthma. *Chest* 2010; 137: 1417–1426.
7. Myers TR, Tomasio L. Asthma: 2015 and beyond. *Respir Care* 2011; 56: 1389–1410.
8. Wahn U, Lau S, Bergmann R, *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99: 763–769.
9. Corver K, Kerkhof M, Brussee JE, *et al.* House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006; 17: 329–336.
10. Lau S, Illi S, Sommerfeld C, *et al.* Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; 356: 1392–1397.
11. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003; 58: 489–493.
12. Sporik R, Holgate ST, Platts-Mills TA, *et al.* Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990; 323: 502–507.
13. Cullinan P, MacNeill SJ, Harris JM, *et al.* Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004; 59: 855–861.
14. Chan-Yeung M, Ferguson A, Watson W, *et al.* The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol.* 2005; 116: 49–55.
15. Horak F Jr, Matthews S, Ihorst G, *et al.* Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study – 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004; 34: 1220–1225.

16. Custovic A, Simpson BM, Simpson A, *et al.* Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during the first year of life: a randomised trial. *Lancet* 2001; 358: 188–193.
17. Woodcock A, Lowe LA, Murray CS, *et al.* Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; 170: 433–439.
18. Hesselmar B, Aberg N, Aberg B, *et al.* Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999; 29: 611–617.
19. Remes ST, Castro-Rodriguez JA, Holberg CJ, *et al.* Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001; 108: 509–515.
20. Muraro A, Dreborg S, Halken S, *et al.* Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. *Pediatr Allergy Immunol* 2004; 15: 103–111.
21. Muraro A, Dreborg S, Halken S, *et al.* Dietary prevention of allergic diseases in infants and small children: Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004; 15: 291–307.
22. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006; 3: CD000133.
23. Vance GH, Grimshaw KE, Briggs R, *et al.* Serum ovalbumin specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. *Clin Exp Allergy* 2004; 34: 1855–1861.
24. van Odijk J, Kull I, Borres MP, *et al.* Breast feeding and allergic disease: a multidisciplinary review of the literature (1996–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003; 58: 833–843.
25. Sears MR, Greene JM, Willan AR, *et al.* Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360: 901–907.
26. Lau S, Wahn U. Asthma at school age and in adolescence. *Eur Respir Monogr* 2012; 56: 40–48.
27. Lau S. Role of allergen exposure on the development of asthma in childhood. *Eur Respir Monogr* 2012; 56: 128–133.
28. Brand PL, Baraldi E, Bisgaard H, *et al.* Definition., assessment and treatment of wheezing disorders in preschool children: an evidence based approach. *Eur Respir J* 2008; 32: 1096–1110.
29. Castro-Rodriguez JA, Rodriguez-Martinez CE, Custovic A. Infantile and preschool asthma. *Eur Respir Monogr* 2012; 56: 10–21.
30. Schultz A, Devadason SG, Savenije OE, *et al.* The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010; 99: 56–60.
31. Castro-Rodrigues JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and pre-schoolers with recurrent wheezing and asthma. *Pediatrics* 2009; 123: e519–e525.
32. Jackson DJ, Gangnon RE, Evans MD, *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 187: 667–672.
33. Bisgaard H, Hermansen MN, Loland L, *et al.* Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; 354: 1998–2005.
34. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2005; 354: 1985–1997.
35. Murray CS, Woodcock A, Langley SJ, *et al.* Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (IFWIN): double-blind randomised, controlled study. *Lancet* 2006; 368: 754–762.
36. Zeiger RS, Mauger D, Bacharier LB, *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365: 1990–2001.
37. Carlsen K-H, Lødrup-Carlsen KC. Physical exercise, training and sports in asthmatic children and adolescents. *Eur Respir Mongr* 2012; 56: 49–58.
38. Roukema J, Gerrits P, Merkus P. Airway hyperresponsiveness in children. *Eur Respir Monogr* 2012; 56: 158–171.
39. Haahtela T, Järvinen M, Kava T, *et al.* Comparison of β_2-agonist, terbutaline with an inhaled corticosteroid budesonide in newly detected asthma. *N Engl J Med* 1991; 325: 388–392.
40. Kerstjens HA, Brand PL, Hughes MD, *et al.* A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. Dutch Chronic Non-Specific Lung Disease Study Group. *N Engl J Med* 1992; 327: 1413–1419.
41. Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, *et al.* Effects of 22 months of treatment with inhaled corticosteroids and/or β_2-agonists on lung function airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992; 146: 547–554.
42. Waalkens HJ, van Essen-Zandvliet EE, Hughes MD, *et al.* Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioriation. *Am Rev Respir Dis* 1993; 148: 1252–1257.
43. Haahtela T, Jarvinen M, Kava T, *et al.* Effects of reducing or discontinuating inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994; 331: 700–705.
44. Strunk RC, Sternberg AL, Szefler SJ, *et al.* Childhood Asthma Management Program (CAMP) Research Group. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr* 2009; 154: 682–687.

45. Lands LC. Inhaled corticosteroids or leukotriene receptor antagonists as first line therapy for asthma: aspects to consider in the light of the pro-con debate. *Paed Respir Rev* 2011; 12: 243–244.
46. Turpeinen M, Nikander K, Pelkonen AS, *et al.* Daily *versus* as needed inhaled corticosteroid for mild persistent asthma (The Helsinki Early Intervention Childhood Asthma Study). *Arch Dis Child* 2008; 93: 654–659.
47. Martinez FD, Chinchilli VM, Morgan WJ, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised double-blind, placebo-controlled trial. *Lancet* 2011; 377: 650–657.
48. Van Asperen PP. That ICS should be the first line therapy for asthma – con. *Paed Respir Rev* 2011; 12: 250–252.
49. Klok T, de Groot EP, Brouwer AFJ, *et al.* Follow-up of children with asthma. *Eur Respir Monogr* 2012; 56: 210–223.
50. Brand PLP. Inhaled corticosteroids should be the first line of treatment for children with asthma. *Paed Respir Rev* 2011; 12: 245–249.
51. De Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012; 185: 12–23.
52. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000; 343: 1054–1063.
53. Sorkness CA, Lemanske RF Jr, Mauger DT, *et al.* Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007; 119: 64–72.
54. Fineman EH. The use of suprarenal cortex extract in the treatment of bronchial asthma. *J Allergy* 1933; 4: 182.
55. Brown HM, Storey G, George WH. Beclomethasone diproprionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1972; 1: 585–590.
56. Malmstrom K, Rodriguez-Gomez G, Guerra J, *et al.* Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999; 130: 487–495.
57. Onhoj J, Thorsson L, Bisgaard H. Lung deposition of inhaled drugs increases with age. *Am J Respir Crit Care Med* 2000; 162: 1819–1822.
58. Tal A, Golan H, Grauer N, *et al.* Deposition of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996; 128: 479–484.
59. Pauwels RA, Pedersen S, Busse WW, *et al.* Early intervention with budesonide in mild persistent asthma: a randomized double-blind trial. *Lancet* 2003; 361: 1071–1076.
60. Beck-Ripp J, Griese M, Arenz S, *et al.* Changes of exhaled nitric oxide during steroid treatment of childhood asthma. *Eur Respir J* 2002; 19: 1015–1019.
61. Check WA, Kaliner MA. Pharmacology and pharmacokinetics of topical corticosteroids derivatives used for asthma therapy. *Am Rev Respir Dis* 1990; 141: S44–S51.
62. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother* 2009; 43: 519–527.
63. Currie GP. Chapter 4. Pharmacological management and inhalers. *In*: Currie GP, ed. Asthma. Oxford, Oxford University Press, 2008.
64. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010; 36: 671–668.
65. Boogaard R, Huijsmans SH, Pijnenburg MW, *et al.* Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. *Chest* 2005; 128: 3391–3397.
66. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004; 24: 822–833.
67. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005; 94: 366–371.
68. Verberne AA, Frost C, Roorda RJ, *et al.* One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med* 1997; 156: 688–695.
69. Castle W, Fuller R, Hall J, *et al.* Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993; 306: 1034–1037.
70. Pauwels RA, Lofdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formeterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337: 1405–1411.
71. Bateman ED, Boushey HA, Bousquet J, *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study. *Am J Respir Crit Care Med* 2004; 170: 836–844.
72. Stanford RH, Fuhlbrigge A, Riedel A, *et al.* An observational study on fixed dose combination fluticasone propionate/salmeterol or fluticasone propionate alone on asthma-related outcomes. *Curr Med Res Opin* 2008; 24: 3141–3148.
73. Rottier BL, Janssen H, de Jongste JC. Guideline treatment of asthma in children: three controversial treatment options. *Ned Tijdschr Geneesk* 2012; (In press.)
74. Lemanske RF Jr, Mauger DT, Sorkness CA, *et al.* Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010; 362: 975–985.
75. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med* 2011; 364: 2473–2475.

76. Papi A, Paggiaro PL, Nicolini G, *et al.* Beclomethasone/formoterol *versus* budesonide/formoterol combination therapy in asthma. *Eur Respir J* 2007; 29: 682–689.
77. Adcock IM, Gilbey T, Gelder CM, *et al.* Glucocorticoid receptor localization in normal and asthmatic lung. *Am J Respir Crit Care Med* 1996; 10: 771–782.
78. Lahzami S, King GG. Targeting small airways in asthma: the new challenge of inhaled corticosteroid treatment. *Eur Respir J* 2008; 31: 1145–1147.
79. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β_2-agonist particle size. *Am J Respir Crit Care Med* 2005; 172: 1497–1504.
80. Rottier BL, de Boer AH, Duiverman EJ. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: three areas for future research. Which areas to target? Which particle size to deliver? Which device to use? *J Cyst Fibros* 2010; 9: 296–297.
81. De Vries TW, Rottier BL, Gjaltema D, *et al.* Comparative *in vitro* evaluation of four corticosteroid metered dose inhalers: consistency of delivered dose and particle size distribution. *Respir Med* 2009; 103: 1167–1173.
82. Blake K, Madabushi R, Derendorf H, *et al.* Population pharmacodynamic model of bronchodilator response to inhaled albuterol in children and adults with asthma. *Chest* 2008; 134: 981–989.
83. Israel E. Genetics and the variability of treatment response in asthma. *J Allergy Clin Immunol* 2005; 115: Suppl. 4, S532–S538.
84. Ye YM, Lee HY, Kim SH, *et al.* Pharmacogenetic study of the effects of NK2R G231E G>A and TBX21 H33Q C>G polymorphisms on asthma control with inhaled corticosteroid treatment. *J Clin Pharm Ther* 2009; 34: 693–701.
85. Newman S, Fleming J. Challenges in assessing regional distribution of inhaled drug in the human lungs. *Expert Opin Drug Deliv* 2011; 8: 841–855.
86. Blake K, Mehta R, Spencer T, *et al.* Bioavailability of inhaled fluticasone propionate *via* chambers/masks in young children. *Eur Respir J* 2012; 39: 97–103.
87. Janssens HM, Krijgsman A, Verbraak TF, *et al.* Determining factors of aerosol deposition for four pMDI-spacer combinations in an infant upper airway model. *J Aerosol Med* 2004; 17: 51–61.
88. De Lange EE, Altes TA, Patrie JT, *et al.* Evaluation of asthma with hyperpolarized helium-3 MRI: correlation with clinical severity and spirometry. *Chest* 2006; 56: 1055–1062.
89. Van Beek EJ, Dahmen AM, Stavngaard T, *et al.* Hyperpolarised ^{3}He MRI *versus* HRCT in COPD and normal volunteers: PHIL trial. *Eur Respir J* 2009; 34: 1311–1321.
90. Goldberg S, Elnot T, Algur N, *et al.* Adrenal suppression in asthmatic children receiving low-dose inhaled budesonide: comparison between dry powder inhaler and pressurized metered-dose inhaler attached to a spacer. *Ann Allergy Asthma Immunol* 2002; 89: 566–571.
91. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet* 2011; 377: 1032–1045.
92. Laube BL, Janssens HM, de Jongh FH, *et al.* What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011; 37: 1308–1331.
93. Burgess SW, Sly PD, Morawska A, *et al.* Assessing adherence and factors associated with adherence in young children with asthma. *Respirology* 2008; 13: 559–563.
94. Sly PD, Jones CM. New and future developments of therapy for asthma in children. *Eur Respir Monogr* 2012; 56: 224–234.

Chapter 18

Follow-up of children with asthma

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SUMMARY: Although (near) total asthma control is possible using currently available medication, asthma remains poorly or partly controlled in many children. Poor adherence to treatment (including poor inhalation technique) is the main reason for this paradox, followed by ongoing exposure to environmental triggers and relevant comorbidity. During follow-up of children with asthma, the medical team should therefore focus on factors potentially hampering asthma control. Forging and maintaining a partnership with patients and parents is of paramount importance. Such a partnership should aim at shared decision making, taking the patient's and parents' illness and medication perceptions, and their treatment goals and preferences into account. Asthma education should be aimed at developing self-management, not transferring knowledge. By discussing and assessing adherence and control at every follow-up visit, aligning with the goals and preferences of the patients and their parents, identifying and treating relevant comorbidity, and by involving asthma nurses and allied health professionals as needed, asthma can be successfully and consistently controlled in the large majority of children.

KEYWORDS: Adherence, asthma control, comorbidity, illness perceptions, physician–patient communication, self-management

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This chapter will provide a thorough overview of the evidence on diagnosing, monitoring and treating childhood asthma. Although one would assume that such up-to-date knowledge should be sufficient to obtain good asthma control in most children with asthma, clinical reality is different: recent surveys consistently show that the burden of asthma is still considerable in children [1–3]. At the same time, however, evidence is emerging that well-controlled asthma can be obtained in most children receiving comprehensive asthma care [4, 5]. In this chapter, we discuss the keystones of such successful asthma care. The starting point of our discussion is the reality that patients and their parents (and not doctors) make day-to-day decisions about managing the child's asthma. Therefore, we introduce and discuss the concept of self-management in childhood asthma and its implications for the doctor–patient partnership. Understanding the role of children and their parents in obtaining good asthma control is the key for successful asthma management. Self-management education and adherence to therapy is also discussed, and

later we focus on assessing asthma control and what to do when asthma is not well-controlled and nonadherence is excluded. Finally, we show that comprehensive asthma care involves a team effort, including input from asthma nurses and psychologists.

Self-management

> *''Self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition''* [6].

The need for patients and their parents to take an active role in the management of asthma is inherent in this condition, not least because the as-needed use of relievers relies on the patient's and parents' judgment [7]. Patients and their parents need to be able to self-monitor the child's asthma in order to use reliever medication reliably, recognise deterioration of the disease and manage exacerbations. To prevent asthma attacks, patients should know how to avoid or control triggers. Although self-management comprises much more than the aforementioned skills, it already becomes clear that patients and parents have to take many day-to-day decisions on their own. Effective self-management requires such day-to-day decisions to be concordant with the advice offered by the medical team (fig. 1). However, all patients (or their parents) construct lay theories (sometimes referred to as the ''Common Sense Model'') that comprise their perceptions of their illness and the medications prescribed to them [8–10]. These views are formed not only in response to what physicians tell patients, but are also based on information patients obtain from informal sources such as the internet, television programmes, fellow patients, family and friends. Research has shown that these illness perceptions and medication perceptions strongly determine self-management behaviour [9]. This is why day-to-day decisions made by patients and their parents can differ considerably from the advice offered by the medical team (fig. 1) [10].

As stated by COULTER and ELLINS [11] ''It used to be assumed that doctors and patients shared the same goals, but only the doctor was sufficiently informed and experienced to decide on the most appropriate course of treatment and how to manage the patient's condition. Patients were seen as ignorant and incompetent in medical matters, so they were expected to trust the doctor and follow medical advice without question''.

Paradigm shift

There has been a paradigm shift and although most healthcare providers will now acknowledge this approach to doctor–patient partnership as outdated, current daily practice frequently does not meet patients' (or parents') needs [11, 12]. For example, parents may not be satisfied when the physician's diagnosis and advice does not match their perceptions about the severity of their child's symptoms [13]. Asthma guidelines, therefore, propose to form a patient–doctor partnership which can be strengthened by discussing and agreeing on treatment goals, and by developing a personalised self-management plan between

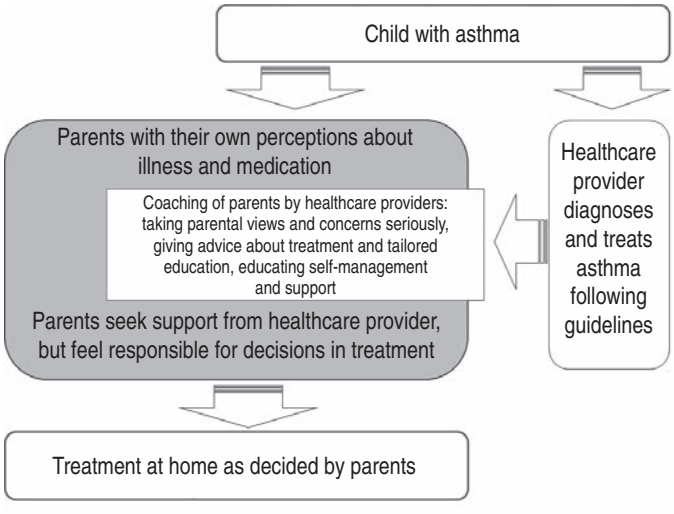
Child with asthma
Parents with their own perceptions about illness and medication
Coaching of parents by healthcare providers: taking parental views and concerns seriously, giving advice about treatment and tailored education, educating self-management and support
Parents seek support from healthcare provider, but feel responsible for decisions in treatment
Healthcare provider diagnoses and treats asthma following guidelines
Treatment at home as decided by parents

Figure 1. The pivotal role of parents in the self-management of childhood asthma.

patients and healthcare professionals [14]. In an ideal world, this is indeed the case. In practice, however, doctors commonly find it difficult to accept that their well-intended medical information and advice meets resistance from children with asthma and their parents [11]. Most doctors have not been trained in patient-centred care or in dealing with resistance, and may be disappointed and frustrated when their recommendations are not being followed [11].

For many physicians, therefore, building and maintaining an effective partnership with asthmatic children and their parents requires a paradigm shift from the medical care they have been trained in. Rather than dispensing advice and prescribing treatment in a hierarchically oriented relationship, they are currently expected to offer patient-centred care, based on a physician–patient partnership requiring an approach based on equality, offering advice as a coach, showing a genuine interest in the patient's values and opinions, and taking these into account to form a mutually agreed management plan [5, 15]. During follow-up, this plan is continuously reviewed and adapted to suit the patient's preferences and needs as much as possible: in the end, it is the patient (and their parents) that decides about maintenance treatment, and not the physician or the guidelines (fig. 1) [13]. Follow-up consultations usually begin with the physician enquiring about the state and control of the patient's asthma, but this may be considerably different from what is most important to patients at that particular time (who may, for example, wish to discuss side-effects of inhaled corticosteroids (ICS), or the child being stigmatised when using their medication at school). Instead of opening a follow-up consultation by asking "how has your asthma been?" (doctor's agenda), one could enquire "what would you like to discuss with me today?" (patient's agenda).

Establishing and maintaining an effective patient–physician partnership

Emerging evidence suggests that an effective partnership between physicians and patients with asthma is of paramount importance in improving adherence to ICS treatment and controlling the disease [9, 16, 17]. In a proof-of-principle study, patient-centred therapy (where doctors and patients actively agreed on treatment goals and medication choices, taking patients' views and preferences explicitly into account) was associated with improved adherence and asthma control when compared with regular care [18]. The patient/parent–physician partnership recommended in asthma guidelines is a prerequisite for successful guided self-management [14]. Although this may seem self-evident, scientific studies and clinical experience clearly show that developing such an effective patient–physician partnership is difficult [19]. This is caused by several factors, one of which was touched on earlier: the physician having to make the paradigm shift from a hierarchically oriented relationship to a patient-centred relationship. Another factor potentially interfering with building a relationship with patients is the organisation of the outpatient asthma care. It has been shown that patients visiting the same healthcare provider during each follow-up visit are more likely to show good medication adherence than patients seen by different team members during subsequent visits [20]. Physician consultations are often characterised by limited time, which may hamper the development and maintenance of a constructive partnership [21]. Last but not least, to establish and maintain an effective patient–physician partnership, the patient–physician communication is of pivotal importance [22, 23]. Most doctors have not been trained in communication techniques needed for patient-centred care, such as shared decision making, discussing parental illness perceptions and medication perceptions and motivational interviewing. Training physicians to communicate better enhances their communication skills and even more importantly, enhances their patients' adherence and improves their patients' asthma control [17, 24, 25]. This relationship between physician communication and adherence to maintenance medication will be explored next.

Self-management education and adherence to maintenance therapy

In clinical trials, asthma in children can usually be well or completely controlled by daily anti-inflammatory maintenance therapy, such as ICS [26]. This is why evidence-based asthma

guidelines recommend ICS as the medication of first choice for the maintenance therapy of chronic asthma in children [14]. In surveys in real-life settings, however, the majority of children with asthma remain symptomatic even when they have been prescribed ICS [3, 27]. Apparently, these children do not take full advantage of the medication that has been prescribed to them. Nonadherence to ICS medication is a major driver of this paradox. Good adherence to ICS is strongly associated with good asthma control, while most cases of children with poor asthma control can be explained by nonadherence to ICS treatment [28, 29]. Therefore, significant efforts to obtain high adherence are worth-while and cost-effective by reducing emergency department visits and hospitalisations [30]. High adherence to maintenance medication is likely to be the key driver of the relationship between well-controlled asthma and comprehensive asthma care mentioned previously [4]. We will discuss this relationship in more detail.

Education of self-management skills

Nonadherence to therapy can be divided into intentional and non-intentional nonadherence [15]. Patients who intentionally do not follow medical advice make their own choices, driven by their perceptions about illness and medication. The approach to such patients is discussed in the next section. Non-intentional nonadherence refers to patients' misunderstanding or forgetting the physician's advice. In childhood asthma, incorrect inhalation technique is a common example of non-intentional nonadherence. In order to achieve and maintain correct inhalation technique, the procedure has to be trained and checked extensively [31, 32]. Other examples of non-intentional nonadherence include the failure to replace an empty canister, and simply forgetting to use the medication, which is more likely in families with a chaotic and disorganised family life [15, 33]. Discussing the use of medicines in detail with patients and their parents and letting them take their medicines to the clinic can reveal such adherence-hampering factors [34]. Nurse-led assessments by home visits can help identify potentially modifiable factors [35]. Although this is time-consuming, it is one of the key components of successful comprehensive asthma care.

Tailored education to modify perceptions about illness and medication

When confronted with patients and parents who intentionally do not adhere to maintenance medication, the first impulse for many physicians is to try and show the patient and parents the errors of their ways, by providing medical information on the disease asthma and its treatment. However, such education of asthma knowledge is of limited value in improving adherence on its own, because (self-management) behaviour is influenced much more strongly by perceptions (including common sense) than by knowledge [36]. An increasing body of evidence indicates that illness perceptions and medication perceptions, the unique and idiosyncratic ideas and beliefs that patients and their parents have about asthma, and its treatment with ICS, are major modifiable determinants of adherence (and nonadherence) in childhood asthma [37, 38]. Many nonadherent adult patients with asthma do not consider asthma to be a chronic condition needing maintenance medication, but rather an episodic condition [39, 40]. This common illness perception may be modified relatively easily by general education about asthma, even when the healthcare provider is not aware of this common sense feeling of the patient. However, many other illness perceptions or medication perceptions are very specific and need tailored education. An example of such a specific illness perception comes from a focus group study in which a father of an asthmatic child compared asthma to a sprained ankle: ''maybe you need crutches first, but for full recovery you have to walk without them'' [13]. The common sense feeling that maintenance therapy prohibited full recovery made this father stop giving ICS to his daughter, to provide her the opportunity to build up ''resistance against asthma''. Medication perceptions are also important drivers of nonadherence [8, 10]. Although patients' concerns about possible side-effects of ICS are the best known example, several other medication perceptions exist and may influence adherence. In our focus group study, for example, the majority of parents expressed a strong general resistance

against giving daily medication to their child (''it doesn't feel right to pump poison into his little body every day'', as one mother put it) [13].

Because of the wide range of possible perceptions about illness and medication, healthcare providers need to actively interview patients and parents about such perceptions, before tailored education can be given to modify them. Although only a few studies have actually studied the modification of perceptions, the little available evidence does indeed suggest that this may be successful [9]. A focus group study from our unit recently showed that parents of children with asthma in primary care had illness and medication perceptions that were inconsistent with the medical model of asthma, and were associated with poor adherence to ICS. Conversely, parents of children treated and followed up at our asthma clinic, after referral by primary care physicians because of difficult-to-control asthma, expressed illness and medication beliefs that were concordant with the medical model of asthma (table 1) [13]. The high self-reported adherence in this group of parents was confirmed when we monitored ICS adherence by electronic logging devices over a 3-month period [41]. These observations led us to conclude that illness and medication beliefs can apparently be modified during long-term treatment in a specialised asthma clinic [13].

Adherence and poorly controlled asthma

Although an effective patient–physician partnership helps to improve adherence and increases the likelihood that patients and their parents openly disclose adherence issues to their physician, nonadherence to therapy remains difficult to rule out [15, 35]; in particular, because nonadherence to ICS is not associated with easily recognisable patient features such as socioeconomic status or asthma severity [20]. As a result, nonadherent patients cannot be recognised reliably by healthcare providers [42]. Therefore, adherence should be discussed in every case of a patient with poorly controlled asthma [43]. However, even in anonymous study settings, self-reported adherence rates have been shown to be unreliable [44]. It can be helpful to assess potential barriers to adherence, including patients' and parents' perceptions about illness and medication, lack of family routines, psychiatric illness of patients or their parents and financial

Table 1. Parental perceptions about asthma and treatment with inhaled corticosteroids (ICS)

Perceptions about asthma and the treatment with ICS inconsistent with the medical model of asthma	Perceptions about asthma and the treatment consistent with the medical model of asthma
''Most illnesses in children disappear by themselves.''	''First I thought that periods with no symptoms means she had control over the asthma by herself and medicines were no longer needed. Now I have learned this is the wrong assumption.''
''If you continue preventive medicine you can never find out whether the child can do without.''	''The well-being of my daughter depends on the use of the medication''
''I compare it with a sprained ankle: maybe you need crutches first, but for full recovery you have to walk without them.''	''Her asthma may not disappear, but with the medicines you can suppress it''
''We wanted to find out how he would do without his medicine. Well, he was fine. So now we only give the medicine when he needs it.''	''The fluticasone is a preventive medicine, I try to say, just take your meds, you can reach the age of one hundred years using them.''
''I don't want to burden my child with medicine of which I am not sure it will help. With salbutamol, it is clear, but with fluticasone, you just have to assume that it works. And that is really difficult.''	''If you are thinking about the kind of medicines you put into your child, sometimes it upsets you, but asthma upsets you more. So, you have to give the medicines.''
''It doesn't work as well when you use it on a daily basis.''	''He uses it on a daily basis, it prevents complaints.''

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problems [15]. Psychological assessment and home visits contribute to detecting factors that keep patients from being adherent [35]. Ultimately, the only really reliable method to assess adherence is to measure it with electronic logging devices [44]. Providing feedback on measured adherence can increase the use of maintenance medication [45].

Asthma control and its assessment

When a partnership is established and self-management skills are taught, joint treatment goals should be defined. These should take the patients' preferences into account. Symptom-based self-management is preferred over home spirometry-based management because it is easier to perform and equally effective.

Definition of asthma control

The main goal of asthma management, as stated by international guidelines, is achieving and maintaining asthma control while avoiding adverse effects of medication [14]. The focus is set on a symptom-based level of asthma control [14]. This is in accordance with current knowledge showing limited value of repeated measurements of lung function or inflammatory markers [46, 47]. Asthma symptoms as the cornerstone for assessing asthma control place the patient's perception of symptoms at the centre of asthma management and emphasises the importance of self-management and self-management education. In this section, we discuss the day-to-day patient's assessment of asthma symptoms, followed by scheduled monitoring of asthma control by healthcare providers.

Day-to-day assessment of control

The self-management of asthma relies heavily on the ability of patients and parents to determine the severity of the disorder on a day-to-day basis, and to respond appropriately. It is commonly assumed that many children are "poor perceivers" of airway obstruction, and that this may hamper symptom-based self-management. Currently available evidence does not support this assumption, however. First, poor perception of airway obstruction is more common in children with undiagnosed asthma than in children with diagnosed asthma [48]. However, in an observational study of home spirometry in children with asthma, we still found poor perception of airway obstruction in 36% of patients, and over-reporting of symptoms (20%) or complete dissociation between symptoms and lung function (25%) very common [49]. But, in a large group of asthmatic children followed up for 1 year, poor perception of dyspnoea was not associated with emergency visits for asthma or poor lung function [50].

In addition, studies examining alternative strategies of monitoring childhood asthma, using peak flow, home spirometry or inflammatory markers such as exhaled nitric oxide, have shown no superiority over symptom-based monitoring [46, 47]. Towards the end of the 20th century, home peak flow monitoring was recommended as a routine procedure in childhood asthma, to overcome the subjective nature of symptom monitoring. This practice was undermined by the discovery that the paper diaries used in such home peak flow monitoring were hopelessly unreliable, with as much as half of the data either invented or incorrectly recorded [51]. The advent of electronic home spirometers was expected to overcome this unreliability [52]. Children show high adherence to home spirometry and perform these measurements in a technically correct manner [53]. However, a randomised trial comparing symptom-based self-management to home spirometer-based self-management in 90 children with asthma found no differences in asthma outcomes over a 3-month period [46]. More recently, a randomised trial comparing asthma management based on daily exhaled nitric oxide measurements to symptom-based management in 151 children with asthma showed no significant differences between groups over a 30-week period [47].

At present, therefore, there is no evidence that monitoring childhood asthma based on "objective" parameters such as lung function or exhaled nitric oxide is superior to monitoring based on

symptoms alone. We therefore recommend symptom-based monitoring, and spend considerable effort in our asthma education and training programmes to help patients and parents to reliably recognise impending deterioration of asthma, and to respond accordingly. The easy accessibility of asthma nurses to help patients and parents in this process has been appreciated by parents as a key success feature of our comprehensive asthma care [54].

Scheduled monitoring of disease activity

Scheduled follow-up of children with asthma is needed to review asthma control and its treatment, discuss patient's and parents' perceptions and concerns, reinforce self-management, and agree on treatment goals and methods for the future. To assess asthma control during such follow-up visits, different paediatric asthma control questionnaires have been developed (Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ) and Asthma Quiz for kids). These assessment instruments are promising and appealing as easy-to-use methods to measure a key concept (asthma control) in asthma management. A web-based asthma control questionnaire which is preferred by parents of asthmatic children has recently been validated [55]. However, before recommending routine use of these instruments, numerous issues require further study. For example, the reliability of asthma control questionnaires to assess asthma control at different ages has not been established [56]. In addition, studies examining the agreement between asthma control measures by these instruments and those assessed by the Global Initiative for Asthma (GINA) or the British Thoracic Society (BTS) criteria have yielded conflicting results [3, 55]. Finally, studies are needed comparing the effects of childhood asthma management based on repeated asthma control questionnaires with traditional symptom-based monitoring.

Although routine spirometry during scheduled follow-up visits is commonly practiced, its value is debatable, because the contribution to obtain asthma control is limited [57]. However, spirometry may help to classify the severity of asthma and degree of asthma control [58, 59]. Most paediatricians will therefore record spirometry in asthmatic children at least once a year [57].

In conclusion, there is no accepted gold standard on how to assess and monitor asthma control in children. We recommend that medical teams not only monitor asthma control by using questionnaires, performing spirometry or by applying GINA or BTS criteria, but also discuss with patients and parents their own perceptions on asthma control and their personal goals in asthma management.

When asthma is not well controlled

When asthma is insufficiently controlled, adherence and self-management should be assessed as the main drivers of uncontrolled asthma (table 2) [28, 29]. When these two factors have been addressed, other attempts should be made to identify the cause of uncontrolled asthma before stepping up therapy. As in adults, asthma is associated with the following comorbid conditions in children, all of which may influence asthma control (table 3) [60].

Table 2. Reasons for poorly controlled or uncontrolled asthma

Very common reasons
Poor adherence to maintenance medication
Poor inhalation technique
Common reasons
Ongoing exposure to environmental stimuli (tobacco smoke, allergens, irritants)
Disease mimicking asthma
Relevant comorbidity (table 3)
Rare reasons
True, therapy-resistant asthma (insufficient maintenance medication)

Obesity

Obesity in children has become an increasing concern, caused by sharply increased obesity rates in children of all ages [61]. Several studies showed higher rates of asthma in overweight children [62, 63], and increased asthma morbidity in overweight asthmatic children [64, 65].

Table 3. Most relevant comorbidities in childhood asthma

Common and relevant	Occasional	Rare/rarely relevant
Overweight/obesity Allergic rhinitis	Dysfunctional breathing Depression and other mental disorders	Gastro-oesophageal reflux

Potential mechanisms for the association between asthma and being overweight include: reduced lung volume and tidal volume promoting narrowing of the airways; low-grade inflammation acting on the lungs to exacerbate symptoms; obesity-related changes in hormones; and comorbidities of obesity itself such as dyslipidaemia, gastro-oesophageal reflux, sleep-disordered breathing, type 2 diabetes, or hypertension that may provoke or worsen asthma [66]. In contradiction to adults, the effects of weight reduction in overweight children on asthma have not been established [67–69]. This is accompanied by the knowledge that weight reduction is difficult to obtain. Nevertheless, we think that in obese children with uncontrolled asthma it is worthwhile to start a weight reduction programme.

Allergic rhinitis

Reported prevalence rates of allergic rhinitis in children with asthma ranges from 60% to 80% [70, 71]. Asthma and allergic rhinitis frequently coexist because of their shared allergic inflammatory pathogenesis and the crosstalk between the nasal and the lower airway epithelium [72]. Symptoms of allergic rhinitis (including nasal itching, sneezing, increasing secretion and a blocked nose) may be missed if patients or parents are not directly questioned about them [73]. In adults, the use of nasal corticosteroids is associated with a significantly reduced risk of asthma-related emergency room treatments and hospitalisations [70, 74]. Although it is likely that adequate treatment of allergic rhinitis can also reduce asthma morbidity in children, this has not been demonstrated in clinical studies to date. We recommend questioning all children with asthma about symptoms of rhinitis and, if needed, prescribing medication, in particular when asthma is not well controlled [73].

Dysfunctional breathing

Dysfunctional breathing is defined as chronic or recurrent changes in breathing pattern, causing respiratory and non-respiratory complaints [75]. Symptoms of dysfunctional breathing include dyspnoea despite normal lung function, deep sighing, exercise-induced breathlessness, frequent yawning and hyperventilation. The prevalence of dysfunctional breathing in asthmatic children is unknown, partly caused by the lack of a validated technique to identify dysfunctional breathing in asthma [75]. In a randomised controlled trial, physiotherapy improved the quality of life in adults with dysfunctional breathing symptoms [76]. Studies on dysfunctional breathing in childhood asthma are largely lacking, although dysfunctional breathing and its overlap with clinical characteristics of asthma has been described in children with exercise-induced breathlessness [77, 78].

Mental disorders

Inaccurate symptom perception, either in the form of under- or over-perception of symptoms may result in poor asthma management or poor control [79]. Higher trait anxiety, for example, is associated with increased perception of asthma symptoms in children, causing overuse of medication [79]. Child and parent negative affect scores and maternal anxiety and depression are associated with increased asthma symptoms, school absence and sleep disturbances [80]. Psychological assessment of children and their caregivers may be required in children with uncontrolled asthma to find potential causes of under- or over-perception of asthma.

Gastro-oesophageal reflux

In children with asthma, the prevalence of gastro-oesophageal reflux disease (GORD) is 23% compared with 4% in healthy controls [81]. Although several other studies confirm such an

association between GORD and asthma, a causal relationship between the two conditions has not been established. Trials of GORD therapy showed no improvement in asthma symptoms in children, although a small study showed a reduction in asthma exacerbations in children with asthma and GORD when treated with a proton-pump inhibitor and a prokinetic agent [82].

Passive smoke exposure

Although the deleterious effects of passive smoking on asthma in children have been established for decades [83], most parents underestimate the effect [84]. Reduction or cessation of exposure to tobacco smoke improves childhood asthma, causing fewer hospitalisations and emergency department visits [85]. Smoking by the primary caregiver and day-care provider are the most important sources of exposure for children with asthma [86]. It is clear that an evaluation of environmental tobacco smoke exposure is mandatory in every child with problematic or uncontrolled asthma.

Teamwork

In our opinion, managing asthma in children is teamwork, in two ways. First, in order to be effective in managing asthma in children, the physician needs to work together as a team with the child and their parents. Secondly, effective asthma management in children does not only involve medical care, but also requires input from other healthcare workers, such as asthma nurses, psychosocial professionals and physical therapists, with whom the physician forms a team to provide optimal care.

Teamwork among healthcare professionals

Because asthma is a highly heterogeneous condition which may not always be easily differentiated from other conditions [14], and because comorbidity in asthma is common and may be serious [60], in our view doctors are indispensable in the diagnosis, treatment and follow-up of asthma in children. We therefore advise against systems of paediatric asthma management that are entirely staffed by nurses or other allied health professionals. We also stress, however, that asthma management provided only by physicians is likely to be less effective than asthma care provided by a dedicated team consisting of doctors, asthma nurses and other allied health professionals. This may be one of the reasons why children treated in specialised clinics have better asthma control [87]. Physician knowledge and experience in diagnosing and treating children with asthma can also contribute to these findings, as training physicians in asthma management has yielded clear benefits for the asthma control of their patients [24].

Role of asthma nurses

There is a large body of evidence supporting the crucial role of specialised nurses in childhood asthma management teams. In children with problematic severe asthma, home visits by asthma nurses revealed treatable comorbidity or complicating factors in the majority of patients that had been missed by medical evaluation alone [35]. In children with mild-to-moderate asthma, it has been shown repeatedly that inhaler technique is poor [88], and that repeated inhalation instruction and demonstration of correct technique are key factors in establishing and maintaining correct inhalation technique [31]. This is a time-consuming task that doctors usually do not have the time for, but asthma nurses do. In addition, parents and children highly value the low threshold availability of asthma nurses, with whom they can discuss issues including fear of side-effects and use of complementary medicine [54]. In children well controlled on ICS, asthma nurses can take on part of the follow-up of children with asthma both effectively and cost effectively [89].

Table 4. Recommendations for successful asthma management

Forge and maintain a partnership with patient and parents based on mutual respect and interest
Take patient's/parents' illness and medication perceptions into account
Identify patient's/parents' treatment goals and preferences
Aim at shared decision making regarding treatment and its goals
Discuss and monitor adherence to treatment and inhalation technique
Teach asthma self-management, not just asthma knowledge
Assess asthma control comprehensively, not just by questionnaire
Identify and treat relevant comorbidity
Establish teamwork with asthma nurses and other allied health professionals

Role of other team members

The high risk of comorbidity [60], in particular psychosocial issues in problematic severe asthma [35], underscores the importance of the availability of mental healthcare professionals in the management of childhood asthma. The relationship between asthma and psychosocial issues is bidirectional, for example, asthma can cause stress and stress can trigger asthma symptoms [90–93]. Effectively addressing psychosocial issues such as bullying [3], social isolation, stress [94], and true psychopathology and behavioural problems [35], may strongly improve asthma control. Such issues should therefore be actively investigated, in particular in children with problematic severe asthma.

(Paediatric) physical therapists may play an important role in diagnosing and treating comorbid breathing abnormalities in children with asthma [60], in encouraging normal physical activity, sports and play in children with asthma [95], and in maintaining optimal physical fitness in these patients [89, 96].

In isolated cases, additional team members such as a paediatric dieticians (in the case of comorbid food allergy or poor energy intake) or an orthopaedic surgeon (in the case of thoracic skeleton abnormalities such as pectus excavatum or scoliosis), may be needed to effectively help children with asthma control their condition. Collaboration and information exchange between medical echelons (between primary and secondary or tertiary care physicians, for example) is also a common issue in asthma management in children. We would like to emphasise that irrespective of the individual members of the team, it is the collaboration within the team that helps to maximise the effects of each team member's input on the management of the child with asthma involved. Only if all healthcare professionals work together as a team will their knowledge and skills be used to their full potential in controlling asthma in children.

Conclusions

Childhood asthma can be well treated and controlled. Although the research field on factors contributing to successful asthma management is rapidly evolving, a number of recommendations can be derived from the literature available to date (table 4). These require time, a team effort, and a genuine interest in what drives patients and parents in their behaviour towards the child's disease. Future studies on asthma management should focus on these key management issues, in addition to traditional experiments aimed at unravelling the pathophysiology of the disease and clinical trials to assess the effectiveness of medication.

Statement of Interest
None declared.

References

1. de Blic J, Boucot I, Pribil C, *et al.* Control of asthma in children: still unacceptable? A French cross-sectional study. *Respir Med* 2009; 103: 1383–1391.

2. Kuehni CE, Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. *Eur Respir J* 2002; 20: 880–889.
3. Carroll WD, Wildhaber J, Brand PLP. Parent misperception of control in childhood/adolescent asthma: the Room to Breathe survey. *Eur Respir J* 2012; 39: 90–96.
4. Scott L, Morphew T, Bollinger ME, *et al.* Achieving and maintaining asthma control in inner-city children. *J Allergy Clin Immunol* 2011; 117: 563–570.
5. Janson SL, McGrath KW, Covington JK, *et al.* Individualized asthma self-management improves medication adherence and markers of asthma control. *J Allergy Clin Immunol* 2009; 123: 840–846.
6. Barlow J, Wright C, Sheasby J, *et al.* Self-management approaches for people with chronic conditions: a review. *Patient Educ Couns* 2002; 48: 177–187.
7. Brouwer AF, Brand PL, Roorda RJ, *et al.* Airway obstruction at time of symptoms prompting use of reliever therapy in children with asthma. *Acta Paediatr* 2010; 99: 871–876.
8. Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychol Health* 2002; 17: 17–32.
9. Kaptein AA, Hughes BM, Scharloo M, *et al.* Illness perceptions about asthma are determinants of outcome. *J Asthma* 2008; 45: 459–464.
10. Conn KM, Halterman JS, Lynch K, *et al.* The impact of parents' medication beliefs on asthma management. *Pediatrics* 2007; 120: 521–526.
11. Coulter A, Ellins J. Changing attitudes to the role of patients in health care. *In*: Newman S, Steed L, Mulligan K, eds. Chronic Physical Illness: Self-Management and Behavioural interventions. Berkshire, McGraw-Hill, 2009; pp. 28–44.
12. Canonica GW, Baena-Cagnani CE, Blaiss MS, *et al.* Unmet needs in asthma: Global Asthma Physician and Patient (GAPP) Survey: global adult findings. *Allergy* 2007; 62: 668–674.
13. Klok T, Brand PL, Bomhof-Roordink H, *et al.* Parental illness perceptions and medication perceptions in childhood asthma, a focus group study. *Acta Paediatr* 2011; 100: 248–252.
14. Global Initiative for Asthma. Global Strategy for asthma management and prevention. 2011. www.ginasthma.org Date last accessed: January 2012. Date last updated: December 2011.
15. Weinstein AG. The potential of asthma adherence management to enhance asthma guidelines. *Ann Allergy Asthma Immunol* 2011; 106: 283–291.
16. Arbuthnott A, Sharpe D. The effect of physician-patient collaboration on patient adherence in non-psychiatric medicine. *Patient Educ Couns* 2009; 77: 60–67.
17. Zolnierek KB, DiMatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care* 2009; 47: 826–834.
18. Wilson SR, Strub P, Buist AS, *et al.* Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med* 2010; 181: 566–577.
19. Weiner SJ, Schwartz A, Weaver F, *et al.* Contextual errors and failures in individualizing patient care: a multicenter study. *Ann Intern Med* 2010; 153: 69–75.
20. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr 200*, 30: 574–582.
21. Braddock CH, Snyder L. The doctor will see you shortly. The ethical significance of time for the patient-physician relationship. *J Gen Intern Med* 2005; 20: 1057–1062.
22. Mauksch LB, Dugdale DC, Dodson S, *et al.* Relationship, communication, and efficiency in the medical encounter: creating a clinical model from a literature review. *Arch Intern Med* 2008; 168: 1387–1395.
23. Roter DL, Hall JA. Communication and adherence: moving from prediction to understanding. *Med Care* 2009; 47: 823–825.
24. Clark NM, Cabana M, Kaciroti N, *et al.* Long-term outcomes of physician peer teaching. *Clin Pediatr (Phila)* 2008; 47: 883–890.
25. de Ridder DT, Theunissen NC, van Dulmen SM. Does training general practitioners to elicit patients' illness representations and action plans influence their communication as a whole? *Patient Educ Couns* 2007; 66: 327–336.
26. Anderson M, Thomas DA. Drug therapy for chronic asthma in children. *Arch Dis Child Educ Pract Ed* 2010; 95: 145–150.
27. Rabe KF, Adachi M, Lai CK, *et al.* Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004; 114: 40–47.
28. Stanford RH, Gilsenan AW, Ziemiecki R, *et al.* Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). *J Asthma* 2010; 47: 257–262.
29. Kruzick T, Covar RA, Gleason M, *et al.* Does access to care equal asthma control in school-age children? *J Allergy Clin Immunol* 2009; 124: 381–383.
30. Kelly CS, Morrow AL, Shults J, *et al.* Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in medicaid. *Pediatrics* 2000; 105: 1029–1035.

31. Kamps AW, Brand PL, Roorda RJ. Determinants of correct inhalation technique in children attending a hospital-based asthma clinic. *Acta Paediatr* 2002; 91: 159–163.
32. Walia M, Paul L, Satyavani A, *et al.* Assessment of inhalation technique and determinants of incorrect performance among children with asthma. *Pediatr Pulmonol* 2006; 41: 1082–1087.
33. Fiese BH, Everhart RS. Medical adherence and childhood chronic illness: family daily management skills and emotional climate as emerging contributors. *Curr Opin Pediatr* 2006; 18: 551–557.
34. Bender BG. Overcoming barriers to nonadherence in asthma treatment. *J Allergy Clin Immunol* 2002; 109: Suppl. 6, S554–S559.
35. Bracken M, Fleming L, Hall P, *et al.* The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child* 2009; 94: 780–784.
36. Dean AJ, Walters J, Hall A. A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. *Arch Dis Child* 2010; 95: 717–723.
37. Kaptein AA, Klok T, Moss-Morris R, *et al.* Illness perceptions: impact on self-management and control in asthma. *Curr Opin Allergy Clin Immunol* 2010; 10: 194–199.
38. Smith LA, Bokhour B, Hohman KH, *et al.* Modifiable risk factors for suboptimal control and controller underuse among children with asthma. *Pediatrics* 2008; 122: 760–769.
39. Halm EA, Mora P, Leventhal H. No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest* 2006; 129: 573–580.
40. Loignon C, Bedos C, Sevigny R, *et al.* Understanding the self-care strategies of patients with asthma. *Patient Educ Couns* 2009; 75: 256–262.
41. Klok T, Kaptein AA, Duiverman EJ, *et al.* Determinants of adherence to inhaled corticosteroids in children with asthma. *Eur Respir J* 2010; 36: Suppl. 54, 473S.
42. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; 353: 487–497.
43. Hedlin G, Bush A, Lødrup Carlsen K, *et al.* Problematic severe asthma in children, not one problem but many: a GA^{2}LEN initiative. *Eur Respir J* 2010; 36: 196–201.
44. Jentzsch NS, Camargos PA, Colosimo EA, *et al.* Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy* 2009; 64: 1458–1462.
45. Burgess SW, Sly PD, Devadason SG. Providing feedback on adherence increases use of preventive medication by asthmatic children. *J Asthma* 2010; 47: 198–201.
46. Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2004; 170: 606–612.
47. de Jongste JC, Carraro S, Hop WC, *et al.* Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; 179: 93–97.
48. van Gent R, van Essen-Zandvliet LE, Rovers MM, *et al.* Poor perception of dyspnoea in children with undiagnosed asthma. *Eur Respir J* 2007; 30: 887–891.
49. Brouwer AFJ, Roorda RJ, Brand PLP. Home spirometry and asthma severity in children. *Eur Respir J* 2006; 28: 1131–1137.
50. Feldman JM, McQuaid EL, Klein RB, *et al.* Symptom perception and functional morbidity across a 1-year follow-up in pediatric asthma. *Pediatr Pulmonol* 2007; 42: 339–347.
51. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. *Thorax* 2001; 56: 180–182.
52. Sly PD, Flack F. Is home monitoring of lung function worthwhile for children with asthma? *West J Med* 2001; 175: 344–345.
53. Wensley DC, Silverman M. The quality of home spirometry in school children with asthma. *Thorax* 2001; 56: 183–185.
54. Kamps AW, Brand PL, Kimpen JL, *et al.* Outpatient management of childhood asthma by paediatrician or asthma nurse: randomised controlled study with one year follow up. *Thorax* 2003; 58: 968–973.
55. Koolen BB, Pijnenburg MW, Brackel HJ, *et al.* Validation of a web-based version of the asthma control test and childhood asthma control test. *Pediatr Pulmonol* 2011; 46: 941–948.
56. van den Bemt L, van Bragt S, Schermer T. The Asthma Control Questionnaire for children: still more questions than answers. *Eur Respir J* 2011; 37: 1534.
57. Brand PL, Roorda RJ. Usefulness of monitoring lung function in asthma. *Arch Dis Child* 2003; 88: 1021–1025.
58. Stout JW, Visness CM, Enright P, *et al.* Classification of asthma severity in children: the contribution of pulmonary function testing. *Arch Pediatr Adolesc Med* 2006; 160: 844–850.
59. Fuhlbrigge AL, Weiss ST, Kuntz KM, *et al.* Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics.* 2006; 118: 347–355.
60. de Groot EP, Duiverman EJ, Brand PLP. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010; 36: 671–678.
61. Kopel SJ, Klein RB. Childhood asthma and obesity. *Med Health R I* 2008; 91: 161–164.
62. Schaub B, von Mutius E. Obesity and asthma, what are the links? *Curr Opin Allergy Clin Immunol* 2005; 5: 185–193.

63. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, *et al.* Increased incidence of asthma-like symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; 163: 1344–1349.
64. Belamarich PF, Luder E, Kattan M, *et al.* Do obese inner-city children with asthma have more symptoms than non-obese children with asthma? *Pediatrics* 2000; 1106: 1436–1441.
65. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001; 56: Suppl. 2, ii64–ii73.
66. Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol* 2008; 121: 1087–1093.
67. Stenius-Aarniala B, Poussa T, Kvarnstrom J, *et al.* Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000; 320: 827–832.
68. Reilly JJ, Methven E, McDowell ZC, *et al.* Health consequences of obesity. *Arch Dis Child* 2003; 88: 748–752.
69. Whitlock EP, Williams SB, Gold R, *et al.* Screening and interventions for childhood overweight: a summary of evidence for the US Preventive Services Task Force. *Pediatrics* 2005; 116: 125–144.
70. Hamouda S, Karila C, Connault T, *et al.* Allergic rhinitis in children with asthma: a questionnaire-based study. *Clin Exp Allergy* 2008; 38: 761–766.
71. Masuda S, Fujisawa T, Katsumata H, *et al.* High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol* 2008; 19: 517–522.
72. Braunstahl GJ. The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease. *J Allergy Clin Immunol* 2005; 115: 142–148.
73. de Groot H, Brand PL, Fokkens WF, *et al.* Allergic rhinoconjunctivitis in children. *BMJ* 2007; 335: 985–988.
74. Corren J, Manning BE, Thompson SF, *et al.* Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004; 113: 415–419.
75. Morgan MD. Dysfunctional breathing in asthma: is it common, identifiable and correctable? *Thorax* 2002; 57: Suppl. 2, II31–II35.
76. Thomas M, McKinley RK, Freeman E, *et al.* Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003; 58: 110–115.
77. Hammo AH, Weinberger MM. Exercise-induced hyperventilation: a pseudoasthma syndrome. *Ann Allergy Asthma Immunol* 1999; 82: 574–578.
78. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005; 94: 366–371.
79. Chen E, Hermann C, Rodgers D, *et al.* Symptom perception in childhood asthma: the role of anxiety and asthma severity. *Health Psychol* 2006; 25: 389–395.
80. Bender B, Zhang l. Negative affect, medication adherence, and asthma control in children. *J Allergy Clin Immunol* 2008; 122: 490–495.
81. Tolia V, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. *Aliment Pharmacol Ther* 2009; 29: 258–272.
82. Khoshoo V, Haydel R Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. *J Pediatr Gastroenterol Nutr* 2007; 44: 331–335.
83. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. *Thorax* 1999; 54: 469.
84. Baena-Cagnani CE, Gomez RM, Baena-Cagnani R, *et al.* Impact of environmental tobacco smoke and active tobacco smoking on the development and outcomes of asthma and rhinitis. *Curr Opin Allergy Clin Immunol* 2009; 9: 136–140.
85. Gerald LB, Gerald JK, Gibson L, *et al.* Changes in environmental tobacco smoke exposure and asthma morbidity among urban school children. *Chest* 2009; 135: 911–916.
86. Cook DG, Strachan DP. Health effects of passive smoking-10: summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999; 54: 357–366.
87. Bravata DM, Gienger AL, Holty JE, *et al.* Quality improvement strategies for children with asthma: a systematic review. *Arch Pediatr Adolesc Med* 2009; 163: 572–581.
88. Kamps AW, van Ewijk B, Roorda RJ, *et al.* Poor inhalation technique, even after inhalation instructions, in children with asthma. *Pediatr Pulmonol* 2000; 29: 39–42.
89. Vahlkvist S, Inman MD, Pedersen S. Effect of asthma treatment on fitness, daily activity and body composition in children with asthma. *Allergy* 2010; 65: 1464–1471.
90. Marin TJ, Chen E, Munch JA, *et al.* Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. *Psychosom Med* 2009; 71: 378–384.
91. Sandberg S, Paton JY, Ahola S, *et al.* The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356: 982–987.
92. Sandberg S, McCann DC, Ahola S, *et al.* Positive experiences and the relationship between stress and asthma in children. *Acta Paediatr* 2002; 91: 152–158.
93. Sandberg S, Jarvenpaa S, Penttinen A, *et al.* Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 2004; 59: 1046–1051.

94. Long KA, Ewing LJ, Cohen S, *et al.* Preliminary evidence for the feasibility of a stress management intervention for 7- to 12-year-olds with asthma. *J Asthma* 2011; 48: 162–170.
95. van Gent R, van Essen-Zandvliet EE, Klijn P, *et al.* Participation in daily life of children with asthma. *J Asthma* 2008; 45: 807–813.
96. Counil FP, Varray A, Matecki S, *et al.* Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr* 2003; 142: 179–184.

Chapter 19

New and future developments of therapy for asthma in children

Peter D. Sly and Carmen M. Jones

SUMMARY: Treatment of childhood asthma has not changed substantially in recent decades, with no truly new drugs having been introduced since the turn of the last century. Mainstream therapy consists largely of inhaled corticosteroids in combination with β-agonists. Montelukast has a role in treating viral-induced wheeze in younger children and in preventing exercise-induced asthma. Review of the currently registered clinical trials for childhood asthma does not reveal any exciting new drug prospects. In recognition of the generally poor adherence with asthma therapy, a substantial research effort is underway to test strategies designed to improve asthma management with existing medications. Novel drugs with potential activity in asthma are currently being trialled in adults with asthma and some of these may eventually find their way into paediatric use. However, the most exciting advances in childhood asthma are likely to come from trials designed to prevent asthma. While several potential strategies can be identified from epidemiological studies, well conducted randomised clinical trials will be required to determine whether they are effective.

KEYWORDS: Asthma, clinical trials, complementary and alternative medicine, drug development pipeline, prevention of asthma

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Mainstream asthma treatment has not changed substantially in the past decade. Apart from new generation inhaled corticosteroids (ICS), which may or may not have reduced side-effects, the only other novel drugs for treating childhood asthma that have been introduced in the last 25 years have been a montelukast, launched in 1998, and omalizumab, which was launched in 2003. While the appropriate use of currently available drugs does reduce the mortality and morbidity associated with asthma, these drugs do not "cure" asthma or effectively alter the natural course of the disease [1]. A new approach with disease-modifying strategies is required [2, 3]. Many children who are recommended to take regular medication do not receive it regularly, and those who do not take regular medication have poorer asthma control [4]. However, even with good treatment adherence, asthma control with current medications is far from perfect [4–6].

Indeed, the current definition for good control of childhood asthma is a score that is greater than 19, on a 24-point scale, showing that the presence of some asthma symptoms is considered "normal" [7]. This chapter will outline the directions asthma treatment in children is taking. Mainstream therapy will not be considered, as it is not new and is covered elsewhere in this *Monograph*. Recent publications of novel treatment approaches will be reviewed, together with highlights from clinical trial registries to present what is forthcoming. Finally, comments will be made concerning the hopes for future treatment strategies, including approaches to preventing asthma.

Current asthma treatment for children: is anything new?

Unfortunately, little is new in the treatment of asthma for children. Recent publications have reported on the efficacy of montelukast, omalizumab, injection immunotherapy, physical exercise, and complementary and alternative medicines (CAM) in children.

Montelukast

While the major use of montelukast has been in treating young children with a viral-induced wheeze, recent studies have confirmed its efficacy for treating exercise-induced asthma (EIA) [8] and re-examined potential steroid-sparing effects [9]. FOGEL *et al.* [8] reported the results of a multicentre, multinational, randomised, double-blinded, double-dummy study of montelukast or salmeterol for treating EIA in children aged 6–14 years. The study used a crossover design with two 4-week treatment periods, separated by a 2-week washout period. Montelukast, compared with salmeterol, resulted in a decreased fall in lung function (group mean maximal fall in forced expiratory volume in 1 second (FEV_1) 10.6 *versus* 13.8%, $p=0.009$; mean area under the FEV_1 curve for 20 minutes post-exercise 116.0 *versus* 168.8% per minute, $p=0.006$) and a more rapid recovery (median time 6.0 *versus* 11.1 minutes, $p=0.04$). In addition, the FEV_1 response to rescue short-acting β_2-agonist after exercise was greater (103.1% predicted *versus* 100.9% predicted, $p<0.001$). These data show small, but statistically significant, superiority of montelukast over salmeterol for preventing EIA.

SCHUH *et al.* [9] reported the results of a randomised, double-blind, double-dummy, non-inferiority trial in which 130 children aged 2–17 years, with acute mild-to-moderate asthma exacerbations that required oral prednisolone, received 5 days of either montelukast or prednisolone treatment after discharge. Treatment failure, defined as an asthma-related unscheduled visit, hospitalisation or additional systemic steroids within 8 days of the initial discharge, occurred in 7.9% of the prednisolone group and 22.4% of the montelukast group (95% CI 26.5–2.4%). Younger children were more likely to fail on montelukast (OR 4.9, 95% CI 1.66–15.22). Thus, there is no role for montelukast in replacing oral prednisolone for maintenance treatment of acute asthma exacerbations (AAEs) severe enough to require systemic steroids.

Omalizumab

While omalizumab has been in use in adults with asthma for some time, studies are only now defining its role in treating asthmatic children. Omalizumab is a humanised immunoglobulin (Ig)G1 antibody constructed from the constant region of the IgG1κ human framework with a variable sequence of mouse antibody; the commercial product is greater than 95% human and less than 5% mouse antibody. The results of two clinical trials adding omalizumab to standard asthma management have recently been published [10, 11]. KULUS *et al.* [10] reported the results of a pre-specified subgroup analysis of a large randomised, double-blind, placebo-controlled, parallel-group study that recruited children aged between 6 years and less than 12 years from 90 centres in Argentina, Brazil, Canada, Colombia, Poland, South Africa and the USA. Of the 246 children with severe asthma, who were inadequately controlled despite being prescribed high-doses of ICS and long-acting β-agonist (LABA), 166 received omalizumab and 80 received placebo. During a

24-week, fixed-dose, steroid phase, omalizumab reduced the rate of clinically significant AAEs by 34% (0.42 *versus* 0.63, rate ratio (RR) 0.662, 95% CI 0.441–0.995, p=0.047). In the second phase of the trial, where adjustment of inhaled steroid does was allowed, omalizumab was associated with a 63% reduction in exacerbations (p<0.001), giving a 50% reduction over the 52-week treatment period (exacerbation rate 0.73 *versus* 1.44, RR 0.504, 95% CI 0.350, 0.725, p<0.001) [10].

Similar, but somewhat less impressive, results were reported from the Inner-City Anti-IgE Therapy for Asthma (ICATA) study undertaken in 6–20-year-old asthmatics [11]. In this study, omalizumab reduced the number of days with asthma symptoms (reduction of 0.48 days over a 2-week period, p<0.001), reduced the proportion of participants who had one or more acute exacerbations (48.8 *versus* 30.3%, p<0.001) and was associated with a reduction of ICS (109 $\mu g \cdot day^{-1}$, p<0.001). The September ''return to school'' epidemic of AAEs was also prevented by omalizumab in this study [11]. Thus, omalizumab has proven efficacy in preventing AAEs when added to standard asthma therapy. This was also the conclusion of a Cochrane review published in 2006 by WALKER *et al.* [12], which reviewed 14 trials, including a total of 3,143 mild-to-severe allergic asthmatics with high levels of IgE. Omalizumab was generally well tolerated, with the most significant side-effect noted as being anaphylaxis.

Injection immunotherapy

A 2010 update of the Cochrane review on injection immunotherapy for asthma reviewed 88 trials, including 13 new trials [13]. These studies included both children and adults. Overall, the authors reported a significant reduction in asthma symptoms scores (standardised mean difference -0.59, 95% CI -0.83– -0.35) and the need to treat three patients (95% CI 3–5) in order to prevent one deterioration in asthma symptoms, as well as the need to treat four patients to avoid one requiring increased asthma medication [13]. From a safety viewpoint, if 16 patients were treated with injection immunotherapy, one would be expected to develop a local adverse reaction, with one in every nine patients that had been treated developing a systemic reaction (of any severity) [13]. While the review includes studies in both adults and children, there was no attempt to report results in the two age groups separately.

Physical exercise

In an interesting twist on the benefits of physical exercise for children with asthma, ONUR *et al.* [14] undertook a study in treatment-naïve asthmatic children, where they were allocated to pharmacological therapy (ICS) alone (n=15) or in conjunction with an exercise programme (n=15) to determine whether exercise improved pulmonary antioxidant status. When compared with non-asthmatic control children (n=13), children with asthma had indications of oxidative stress, *i.e.* higher levels of plasma malondialdehyde (MDA) and total nitric oxide (NO) and lower levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) at baseline. Asthmatic children in both groups showed reductions in MDA and increases in SOD following treatment. However, only those asthmatics who received the exercise programme as well as ICS showed reductions in NO and an increase in GSH-Px. In addition, the combined therapy was associated with statistically and clinically significant improvements in lung function. The authors concluded that the structured exercise programme resulted in improvements in antioxidative defences, over and above those that resulted from ICS therapy alone. Whether these results can be replicated in other populations, and in larger studies, remains to be determined; however, they do support the use of structured physical exercise programmes as an aid to asthma management in children.

Complementary and alternative medicine

CAM therapies are often popular with parents whose children's asthma is not well controlled by conventional asthma therapy or who fear side-effects, especially with steroid-based therapies. While the evidence base for most CAM therapies is scant, reports of clinical trials of some

therapies have been published recently. WONG *et al.* [15] recently reported a randomised, double-blind, placebo-controlled trial of an oral herbal formulation (CUF2) in 85 children with asthma aged 7–15 years. The primary aim was to show a reduction in the ICS dose, with secondary aims to show a reduction in asthma symptoms. After treatment for 6 months there were no differences in the groups with regard to ICS dose or in asthma severity. A systematic review of chiropractic spinal manipulation failed to show any evidence that this therapy was effective in improving asthma [16]. Evidence that acupuncture-like transcutaneous electric nerve stimulation improves childhood asthma is sparse, with one small open-label trial claiming improvements in the "activity limitation" domain of the paediatric asthma quality of life (QoL) questionnaire, but not in other domains [17].

New therapies in adults: could these be translated to children?

The traditional method of assessing new asthma drugs is for the initial trials to be performed on adults, with subsequent paediatric trials on drugs that "show sufficient promise". The problem with this paradigm is that the nature of childhood and adult asthma is different, *i.e.* drugs destined to fail in adults with chronic disease may be beneficial in children with asthma [18]. A number of "designer drugs" with immunomodulatory activity, targeted against specific components of inflammatory pathways, thought to be important in asthma, continue to be trialled in adult asthma. Recently, examples have included: mepolizumab (monoclonal antibody against interleukin (IL)-5) [19]; MEDI-563 (a humaniaed IgG1κ-isotype monoclonal antibody that binds to the α-chain of the IL-5 receptor) [20]; golimumab (monoclonal antibody against tumour necrosis factor (TNF)-α) [21]; mastinab (a tyrosine kinase inhibitor) [22]; suplatast tosilate (blocks release of T-helper (Th) 2 cytokines) [23]; laropiprant (prostaglandin (PG)D_2 receptor type 1 antagonist) [24]; AMG 317 (IL-4 receptor α-antagonist) [25]; tralokinumab (humanised anti-IL-13 monoclonal antibody) [26]; and pitrakinra (an IL-4 mutein that binds the IL-4 α-chain receptor (IL-4Rα) and blocks both IL-4 and IL-13 mediated inflammation) [27]. Trials of more conventional drugs have also been undertaken in adult asthmatics, these include: tiotropium bromide (long-acting anticholinergic) [28]; phosphodiesterase-4 inhibitors (to increase intracellular cyclic adenosine monophosphate (cAMP) and induce airway smooth muscle relaxation) [29]; and statins (enhance anti-inflammatory effects of corticosteroids) [30]. However, whether any of these agents are trialled in children and eventually join the therapeutic armamentarium available to paediatricians remains to be seen.

Future asthma treatment: what is in the pipeline?

Searching the various clinical trial sites reveals a large amount of clinical trial activity in paediatric asthma. While some trials specifically seek to recruit children, many others overlap into the paediatric age range, setting target recruitment ages at 16–65 years or 12–65 years. However, seeing a trial registered on a clinical trial site does not guarantee that the trial is underway or will actually occur. While the registration of clinical trials is a laudable advance, more attention needs to be paid to keeping trial listings up to date.

The registered clinical trials fall into a number of areas, these include: drug therapy; exercise, nutrition and weight loss; therapeutic devices; education, management support or behavioural modification; anti-allergy strategies; and a variety of miscellaneous strategies.

Trials of drug therapy

While there is a large number of drug therapy trials on childhood asthma currently registered, very few new developments are on offer. Currently, 20 trials are registered for ICS, largely new formulations of existing drugs or existing drugs delivered in new devices, and 19 trials are registered for ICS/LABA combinations in various management strategies. New trials with other marketed drugs include: montelukast (eight trials); macrolides (four trials), anticholinergics (five

trials, mainly with tiotropium); and short-acting β_2-agonists (five trials). 10 trials have been registered using "biologicals", *i.e.* molecules designed to block cytokine receptors, including IL-5, and PGD_2. Three trials have been registered that use proton-pump inhibitors to treat or prevent acid gastro-oesophageal reflux, and one was registered to use a statin to enhance the anti-inflammatory actions of ICS. Few trials have been registered to treat acute asthma; there are four trials using oral steroids and one using magnesium sulphate.

Trials using exercise, nutritional strategies or weight loss

Weight loss, using low-calorie diets with the support from professional dieticians, is the focus of two registered trial. While combined physical exercise, nutritional and behavioural intervention forms the basis of another trial. All the trials seek to reduce body mass index (BMI) and improve lung function. One trial also aims to assess markers of systemic and pulmonary inflammation. All three trials are specifically recruiting children (aged 6–18 years).

Dietary supplementation with vitamin D_3 is being tested in five trials in children. The outcomes being assessed vary and include: improvement in lung function, methacholine responsiveness, time to first upper respiratory infection, and frequency of acute exacerbations of asthma. In total, these trials seek to enrol 1,060 children aged 2–18 years, with another 250 participants aged 16–80 years that overlap into the paediatric age range.

Other dietary supplements to be trialled include orthomolecular therapy (90 participants aged 7–18 years, aim is to reduce ICS use), omega-3-poylunsaturated fatty acids (100 participants aged 12–25 years, aim is to improve asthma control), lactobacillus reuteri (or placebo) added to antileukotrienes (40 participants aged 6–16 years, aim is to reduce asthma exacerbation and asthma symptoms), and co-ingestion of grapefruit juice with montelukast (27 participants aged 15–18 years, aim to increase area under the serum montelukast time curve).

Trials of education, behavioural interventions or asthma management support

While most trials in this area are targeted at children with asthma and their families, a programme aimed at improving the management of asthma in general practice has been trialled in Australia. The Practitioner Asthma Communication and Education (PACE) Australia intervention for general practitioners (GPs) comprised two structured 3-hour interactive sessions, 1 week apart. Eight PACE workshops were held from February 2007 to April 2008 for intervention group GPs. Attendance was set at a maximum of 15 GPs per workshop. The specific aims of the PACE workshops were to improve GP practice in the following key areas: appropriate use of medications; writing an asthma action plan; communication between patient and doctor to improve adherence and patient education; and giving instructions on the correct use of aerosol delivery devices. Prior to initiating the trail, a preliminary study demonstrated that the programme was feasible and acceptable to GPs [31]. The elements of the programme that the GPs found most useful were: components to develop communication skills; case studies; asthma device demonstrations; and a toolkit, which contained a workshop folder with a copy of the workshop slides and handouts, a set of airway models to assist with patient teaching, a variety of spacers and asthma delivery devices, and a peak-flow meter. The results of the trial are keenly awaited.

Interventions currently being trialled include: online modules to be completed once a week, which contain social problem-solving skills (40 participants aged 10–17 years, the aim is to improve psychological well-being and social problem solving skills); individual weekly online contact with a psychologist (40 participants aged 10–15 years, the aim is to increase physical, mental and social well-being); improving asthma education (seven trials with a total of 3,239 participants aged 2–18 years, the aim is to generally improve aspects of asthma control); various telehealth, computerised medical records and electronic reminder devices (12 trials with a total of 7,110 children of all ages participating, the aim is to improve adherence with asthma therapy and to improve aspects of asthma control); behaviour modification programmes (18 trials with a total of

5,726 children of all ages participating, the aim is to improve aspects of asthma control); education/behaviour modifications with an emphasis on reducing tobacco smoke exposure (five trials with a total of 3,324 participants, including females of childbearing age, pregnant females and children with the aim to reduce tobacco smoke exposure, personal smoking and to improve asthma control); and trials of asthma management plans (two trials, 612 participants of all ages with the aim to improve asthma control).

Trials of anti-allergy strategies

Trials registered under this category are quite diverse, ranging from allergen avoidance and deliberate exposure to allergens to induce immunological tolerance, specific allergen immunotherapy, anti-IgE therapy and environmental control measures. This area continues to be one of considerable controversy that is unlikely to be settled by any of the currently registered clinical trials.

Future asthma treatment: where should we be looking?

Neither current treatment for childhood asthma nor anything obvious in the clinical trial pipeline is likely to substantially alter the natural history of childhood asthma. New strategies are needed and a review of asthma therapy is required. Strategies based on our knowledge of how asthma develops and that extend beyond controlling asthma symptoms and preventing exacerbations are required before major advances are likely to be made. As a prelude to this section, a brief review of the origins of asthma is warranted to highlight where potential interventions could be targeted.

Asthma, like most chronic diseases, is likely to arise from a genetically predisposed host being subjected to multiple environmental exposures at critical times during development. Increasingly, researchers are beginning to understand that multiple genetic susceptibilities [32, 33] and gene–environment interactions are likely to contribute to asthma [34]. Data from longitudinal birth, cohorts demonstrate that major risk factors for developing persistent asthma include: wheeze associated with viral respiratory infections in the first years of life [35–37]; delayed immune system maturation [38]; and allergic sensitisation in early life [36, 39]. Evidence is also growing for synergistic interactions between viral respiratory infections and allergic sensitisation early in life, which increase the risk of subsequent asthma [36, 40]. These risk factors are all potentially amenable to modification by existing and potential novel therapeutic interventions, as outlined in figure 1.

Prevention of viral, lower respiratory infections in early life

Specific antiviral strategies

The respiratory viruses most commonly associated with wheezing illnesses in early life are human rhinovirus (HRV) and the respiratory syncytial virus (RSV) [35, 36]. Palivizumab is a humanised monoclonal IgG antibody directed against the F protein of RSV, which has been shown to prevent RSV lower respiratory infections in high-risk infants. A long-term follow-up of an original multicentre study using palivizumab, to prevent wheezing in premature infants, has recently shown a reduction of recurrent wheezing in the preschool years of 68% of those with no family history of asthma, and of 80% in those with no family history of atopy or food allergies [41]. However, there was no apparent protective effect in children with atopic families. The latter data questions the effectiveness of palivizumab for preventing persistent asthma, which is generally associated with atopy and an atopic family history. It is not currently possible to prevent HRV infections with specific antiviral strategies.

Nonspecific antiviral strategies

Oral preparations designed to stimulate the immune system have been in clinical use and trial for a considerable time. Perhaps the best known of these preparations are the various probiotic, prebiotic and pre-probiotic preparations. These have primarily been trialled for prevention of

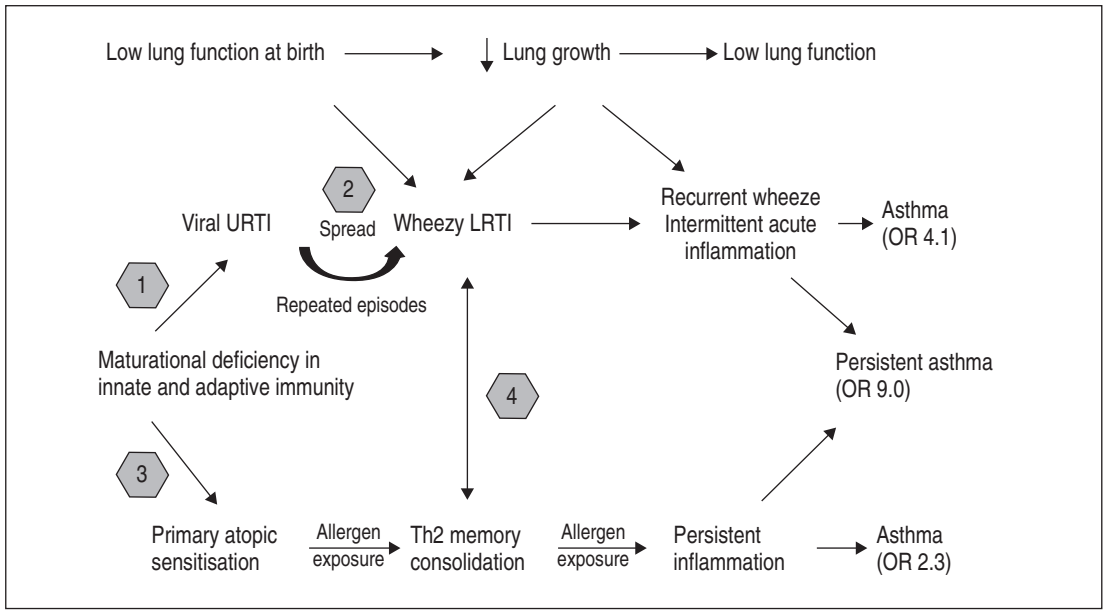

Figure 1. Schematic representation of the major risk factors for persistent asthma. The odds ratios (OR) for persistent asthma at age 6 years are taken from ODDY *et al.* [37]. Two genetic predispositions present at birth *i.e.* maturational deficiency in innate and adaptive immunity and low lung function, are shown together with parallel ''insult'' pathways, *i.e.* recurrent wheezy lower respiratory tract infections (LRTI) and allergic sensitisation in early life. Potential points for preventative strategies are shown. 1) Prevention of viral respiratory infections by specific antiviral strategies. 2) Prevention of viral spread from upper to lower airways. 3) Prevention of primary allergic sensitisation. 4) Interrupting the synergistic interactions between viral induced LRTI and allergic sensitisation in early life. URTI: upper respiratory tract infection; Th: T-helper cell.

atopic dermatitis and have not shown much promise in preventing asthma. In addition, an increase in allergic sensitisation in high-risk infants has been reported [42].

An immunostimulant extracted from eight bacterial pathogens of the upper respiratory tract, OM-85, has been found to be safe and effective in reducing the frequency of upper respiratory tract infections (URTI) in children with a history of recurrent infections [43] and in preventing wheezing attacks in preschool children [44]. This preparation has been in clinical use in Europe for decades and has the potential to be used in primary asthma prevention strategies. If OM-85 is capable of decreasing the frequency of upper respiratory infections and preventing wheezing illnesses, which are associated with lower respiratory viral infections, it has the potential to break the nexus between respiratory viral infections and subsequent asthma.

Preventing viral spread from the upper to lower airways

Respiratory viruses initially infect the upper airway and, if they ''escape'' the antiviral immune surveillance, may spread to the lower airways. Both the innate and adaptive limbs of the immune system are immature at birth and young infants are at an increased risk of lower respiratory illnesses with common respiratory viral infections [45]. In addition, studies in adult volunteers and respiratory epithelial cells *in vitro* suggest that asthmatics may have a primary deficiency of innate antiviral immunity, especially related to deficient secretion of type 1 and type 3 interferons in response to respiratory viral infections [46, 47]. One therapeutic possibility would be to give interferons at the time of a URTI, such trials are underway in adults. However, the systemic effects of interferons are responsible for the ''flu-like'' symptoms experienced during viral infections and, even if this strategy is effective, it may not be acceptable in children.

As outlined previously, OM-85 is effective at preventing wheezing associated with respiratory viral infections in young children [44]. This may occur by preventing the spread of respiratory viruses from the upper to the lower respiratory airways.

Prevention of allergic sensitisation in early life

Early sensitisation is a well-recognised risk factor for persistent asthma [39]; however, despite this, attempts at preventing sensitisation by allergen avoidance have been disappointing, as reviewed by TOVEY and MARKS [48]. Indeed, an understanding of post-natal maturation of the adaptive immune system and how immunological memory is developed would suggest that allergen avoidance is exactly the wrong strategy [45]. HOLT and SLY [49] had previously argued that allergen immunotherapy could be used as a primary prevention strategy. Evidence to support this approach has come from the prevention of sensitisation to "bystander" allergens following allergen-specific sublingual immunotherapy (SLIT) in young children. A small randomised trial, which used a combination of house dust mite, cat and grass allergens as primary prevention, has been completed recently under the strategy name of oral mucosal immunoprophylaxis (OMIP), to differentiate it from SLIT, and its results are eagerly awaited.

Prevention of the synergistic interaction between viral respiratory infections and allergic sensitisation

As noted previously, epidemiological evidence from a variety of cohort studies points to a synergistic interaction between allergic sensitisation in early life and respiratory viral infections. Indeed, in some studies the increased risk of asthma with recurrent viral lower respiratory tract infections (LRTI) is only seen in the presence of early allergic sensitisation [36]. While the mechanism(s) underlying this interaction are uncertain, recent evidence from studying children

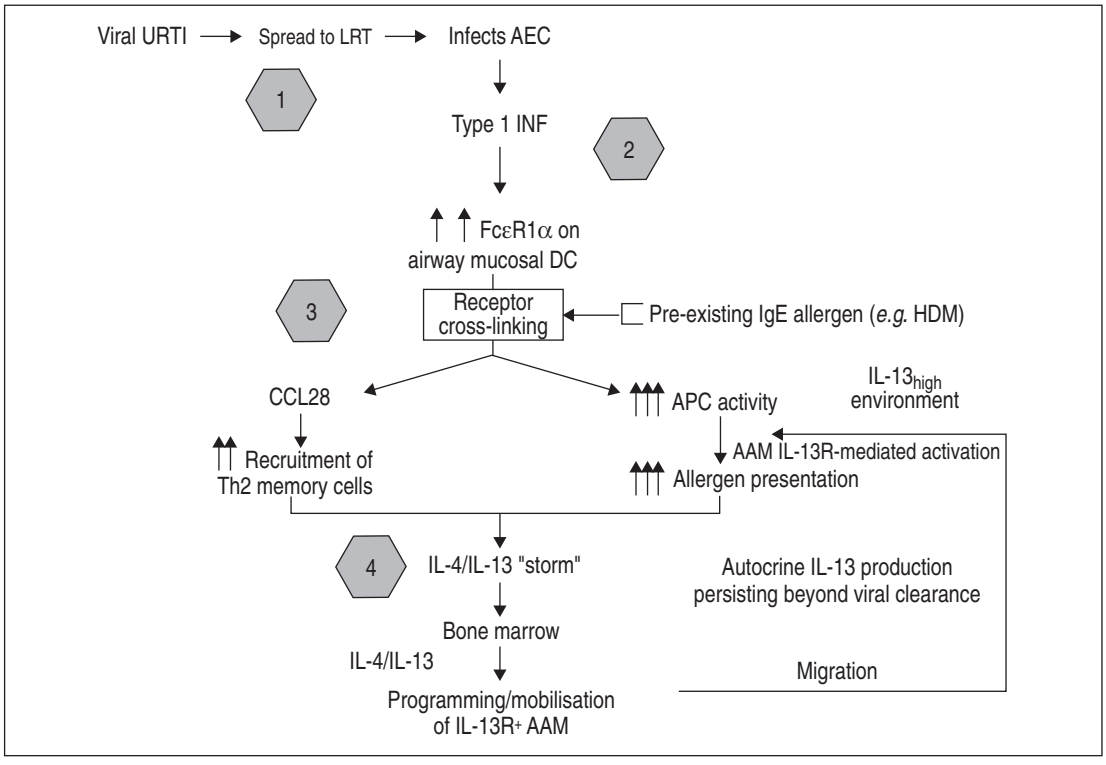

Figure 2. Schematic representation of the lung/bone marrow axis that operates during acute, viral, lower respiratory tract (LRT) infection, amplifying the airway inflammation. The points for potential intervention are: 1) spread of viruses from upper to lower airway; 2) secretion of type 1 interferon (INF) from infected airway epithelial cells (AEC); 3) cross-linking of high-affinity immunoglobulin (Ig)E receptors on airway mucosal dendritic cells (DC); 4) inhibition of the interleukin (IL)-4/IL-13 ''storm''. URTI: upper respiratory tract infection; HDM: house dust mite; FcεR1α: a high-affinity IgE receptor; CCL28: a mucosae-associated epithelial chemokine; APC: antigen presenting cell; AAM: alternatively activated macrophage; Th: T-helper cell.

during acute severe asthma and convalescence may provide some clues [50]. As recently reviewed by HOLT and SLY [51], the operation of a lung/bone marrow axis may not only explain interactions between allergic mechanisms (allergen-specific IgE antibodies and Th 2 memory responses) and viral infections in acute asthma (fig. 2), but also operate during asthma induction. The points for potential intervention are as follows. 1) Spread of viruses from the upper to lower respiratory airway. The potential preventative strategies for this have been outlined previously. 2) Secretion of type 1 interferons from infected airway epithelial cells (AECs). The potential preventative strategies for this are currently subject to active academic research and include attempts to limit viral binding to AECs, enhance apoptosis of AECs in order to limit viral spread, and various strategies to enhance intracellular antiviral immunity. 3) Cross-linking of high-affinity IgE receptors on airway mucosal dendritic cells. Strategies to reduce IgE antibodies could include omalizumab. 4) Inhibiting the IL-4/IL-13 "storm". Pitrakinra binds to the common receptor chain used by both IL-4 and IL-13, therefore, blocking the receptor without activating it could be one possibility.

These targets have not yet been investigated in acute asthma, although trials addressing some of these possibilities are currently in the planning phase. Whether similar mechanisms operate in infants and contribute to the inception of asthma is not known. However, this scenario provides several testable hypotheses that may open new avenues for the primary prevention of asthma.

Conclusion

The natural history of childhood asthma is unlikely to be substantially altered by the therapies currently available for childhood asthma or those being tested in currently registered clinical trials. The evidence base for any of the current CAM therapies in childhood asthma is scant and few trials are currently registered. The way forward appears to be in primary prevention strategies; however, randomised clinical trials need to be based on the increasing data from longitudinal cohort studies that demonstrate the major risk factors for persistent asthma, including lower respiratory viral infections and early allergic sensitisation.

Statement of Interest

None declared.

References

1. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354: 1985–1987.
2. Adcock IM, Caramori G, Chung KF. New targets for drug development in asthma. *Lancet* 2008; 372: 1073–1087.
3. Holgate ST. Novel targets of therapy in asthma. *Curr Opin Pulm Med* 2009; 15: 63–71.
4. Sawicki GS, Strunk RC, Schuemann B, *et al.* Patterns of inhaled corticosteroid use and asthma control in the Childhood Asthma Management Program Continuation Study. *Ann Allergy Asthma Immunol* 2010; 104: 30–35.
5. Rabe KF, Adachi M, Lai CKW, *et al.* Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004; 114: 40–47.
6. Rachelefsky G. Inhaled corticosteroids and asthma control in children: assessing impairment and risk. *Pediatrics* 2009; 123: 353–366.
7. Liu AH, Zeiger R, Sorkness C, *et al.* Development and cross-sectional validation of the childhood asthma control test. *J Allergy Clin Immunol* 2007; 119: 817–825.
8. Fogel RB, Rosario N, Aristizabal G, *et al.* Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. *Ann Allergy Asthma Immunol* 2010; 104: 511–517.
9. Schuh S, Willan AR, Stephens D, *et al.* Can montelukast shorten prednisolone therapy in children with mild to moderate acute asthma? A randomized controlled trial. *J Pediatr* 2009; 155: 795–800.
10. Kulus M, Hébert J, Garcia E, *et al.* Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin* 2010; 26: 1285–1293.
11. Busse WW, Morgan WJ, Gergen PJ, *et al.* Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364: 1005–1015.
12. Walker S, Monteil M, Phelan K, *et al.* Anti-IgE for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2006; 2: CD003559.

13. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8: CD001186.
14. Onur E, Kabaroğlu C, Günay O, *et al.* The beneficial effects of physical exercise on antioxidant status in asthmatic children. *Allergol Immunopathol (Madr)* 2011; 39: 90–95.
15. Wong EL, Sung RY, Leung TF, *et al.* Randomized, double-blind, placebo-controlled trial of herbal therapy for children with asthma. *J Altern Complement Med* 2009; 15: 1091–1097.
16. Ernst E. Spinal manipulation for asthma: a systematic review of randomised clinical trials. *Respir Med* 2009; 103: 1791–1795.
17. Lin CH, Wang MH, Chung HY, *et al.* Effects of acupuncture-like transcutaneous electrical nerve stimulation on children with asthma. *J Asthma* 2010; 47: 1116–1122.
18. Holt PG, Sly PD, Martinez FD, *et al.* Drug development strategies for asthma: in search of a new paradigm. *Nat Immunol* 2004; 5: 695–698.
19. Nair P, Pizzichini MM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–993.
20. Busse WW, Katial R, Gossage D, *et al.* Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol* 2010; 125: 1237–1244e2.
21. Wenzel SE, Barnes PJ, Bleecker ER, *et al.* A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009; 179: 549–558.
22. Humbert M, de Blay F, Garcia G, *et al.* Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. *Allergy* 2009; 64: 1194–1201.
23. Wada M, Nagata S, Kudo T, *et al.* Effect of suplatast tosilate on antileukotriene non-responders with mild-to-moderate persistent asthma. *Allergol Int* 2009; 58: 389–393.
24. Philip G, van Adelsberg J, Loeys T, *et al.* Clinical studies of the DP1 antagonist laropiprant in asthma and allergic rhinitis. *J Allergy Clin Immunol 2009; 124*, 942–948: e1–e9.
25. Corren J, Busse W, Meltzer EO, *et al.* A randomized, controlled, phase 2 study of AMG 317, an IL-4Ralpha antagonist, in patients with asthma. *Am J Respir Crit Care Med* 2010; 181: 788–796.
26. Walsh GM. Tralokinumab, an anti-IL-13 mAb for the potential treatment of asthma and COPD. *Curr Opin Investig Drugs* 2010; 11: 1305–1312.
27. Antoniu SA. Pitrakinra, a dual IL-4/IL-13 antagonist for the potential treatment of asthma and eczema. *Curr Opin Investig Drugs* 2010; 11: 1286–1294.
28. Peters SP, Kunselman SJ, Icitovic N, *et al.* Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363: 1715–1726.
29. Lu S, Liu N, Dass SB, *et al.* Randomized, placebo-controlled study of a selective PDE4 inhibitor in the treatment of asthma. *Respir Med* 2009; 103: 342–347.
30. Maneechotesuwan K, Ekjiratrakul W, Kasetsinsombat K, *et al.* Statins enhance the anti-inflammatory effects of inhaled corticosteroids in asthmatic patients through increased induction of indoleamine 2, 3-dioxygenase. *J Allergy Clin Immunol* 2010; 126: 754–762e1.
31. Shah S, Toelle BG, Sawyer SM, *et al.* Feasibility study of a communication and education asthma intervention for general practitioners in Australia. *Austr J Prim Health* 2010; 16: 75–80.
32. Guerra S, Martinez FD. Asthma genetics: from linear to multifactorial approaches. *Annu Rev Med* 2008; 59: 327–341.
33. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009; 6: 272–277.
34. von Mutius E. Gene-environment interactions in asthma. *J Allergy Clin Immunol* 2009; 123: 3–11.
35. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010; 125: 1178–1187.
36. Kusel MMH, de Klerk NH, Kebadze T, *et al.* Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007; 119: 1105–1110.
37. Oddy WH, de Klerk NH, Sly PD, *et al.* The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; 19: 899–905.
38. Macaubas C, de Klerk NH, Holt BJ, *et al.* Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. *Lancet* 2003; 362: 1192–1197.
39. Sly PD, Boner AL, Björksten B, *et al.* Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; 372: 1100–1106.
40. Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010; 125: 1202–1205.
41. Simoes E, Carbonell-Estrany X, Rieger C, *et al.* The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol* 2010; 126: 256–262.
42. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergic sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007; 119: 184–191.

43. Schaad UB, Mütterlein R, Goffin H. Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind placebo-controlled multicenter study. *Chest* 2002; 122: 2042–2049.
44. Razi C, Harmanci K, Abaci A, *et al.* The immunostimulant OM-85 prevents wheezing attacks in preschool children. *J Allergy Clin Immunol* 2010; 126: 763–769.
45. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. *J Allergy Clin Immunol* 2005; 116: 16–24.
46. Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
47. Wark PA, Johnston SL, Bucchieri F, *et al.* Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005; 201: 937–947.
48. Tovey E, Marks GB. It's time to rethink mite allergen avoidance. *J Allergy Clin Immunol 2011; 128*, 723–727: e6.
49. Holt PG, Sly PD. Prevention of allergic respiratory disease in infants: current aspects and future perspectives. *Curr Opin Allergy Clin Immunol* 2007; 7: 547–555.
50. Subrata LS, Bizzintino J, Mamessier E, *et al.* Interactions between innate antiviral and atopic immuno-inflammatory pathways precipitate and sustain asthma exacerbations in children. *J Immunol* 2009; 183: 2793–2800.
51. Holt PG, Sly PD. Interaction between adaptive and innate immune pathways in the pathogenesis of atopic asthma: operation of a lung/bone marrow axis. *Chest* 2010; 139: 1165–1171.

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